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SYNTHESIS OF NEW PYRIMIDO[1,2-*B*][1,2]THIAZINES AND THIAZINO[3,2-*C*][1,2,4]TRIAZINES

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Abstract
Aseries of pyrimido[1,2-*b*][1,2]thiazinesand thiazino[3,2-*c*][1,2,4]triazineswere successfully synthesized from the reactions of amino-functionalized 1,2-thiazine or its diazonium salt with alkylidene or arylidenemalononitrile, phenols and active methylene reagents. The reactions were found to be highly regioselective. The chemical structures of the new compounds were fully assigned by using different spectroscopic techniques, such as IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis.

Keywords:pyrimidine, thiazine, triazine, alkylidenemalononitrile, arylidenemalononitrile.

Introduction

Bacterial resistance to antibiotics is becoming a serious threat to human health.The development of resistance occurseither directly as a consequence of natural genetic mutationsof bacteria or indirectly due to the misuse or overuse of antibiotics without a medicinal prescription. Recently, twelve bacteria were featured on a priority list released by the WHO (World Health Organization, 2017) and were classified in three categories refereeing to the urgency of findingneweffective antibiotics against them.[I]The three highly troublesome pathogens,*acinetobacterbaumannii*, *pseudomonas aeruginosa* and *enterobacteriaceae*, which resist the carbapenem class of antibiotics, occupied the top of this list. In 2015,around 10.4 million people were infected with tuberculosis and out of them, 1.8 million casesdied.[II] In view of suchworrying statistics, the design and synthesis of potent treatments of bacteria become critically essential.The majority of heterocyclic architectures have been shown to constitute afundamental cornerstone ofthe discovery of newantibacterialdrug.[III-V]In particular,fused heterocyclic systems, which incorp-orate a thiazine central core, were reported toexhibit diverseinteresting pharmacologicalactivities such asanti-inflammatory,[VI-VIII]antibacterial,[IX-XI]anticonvulsant,[XII-XIV]antidiabetic,[XV-XVII]antiviral,[XVIII-XX]antitumor[XXI-XXIII]and analgesic properties.[XXIV-XXVI] In the present study,

we report the synthesis of a series of 1,2-thiazines and their fused derivativeswith pyrimidine's and 1,2,4-triazines which expected to have antimicrobialactivity .

Results and Discussion

Triazineheterocycles were reported to exhibit a wide range of biological activities.[XXVII-XXXI]In continuation to our previous research on exploring the therapeutic potential oftriazines, we reported the synthesis of triazolyl-triazines and their derivatives, which were obtained *via* the copper (I) catalyzed Huisgen alkyne-azidecycloadditionreaction.[XXVII] The 1,3,5-triazine was allocated as central core unit in the reported compoundsdue to its interesting pharmacological activities.[XXVII-XXXI] Sulfur-containingcompounds were reported to possess potent antimicrobial properties.[XXXII]In this contribution, we synthesized a series of pyrimido-thiazines and thiazino-triazines. 1,2-Thiazine **1** was prepared through three component Gwaledreaction[XXXIV] of ethylacetoacetate, urea and sulfur in the presence of piperidineafford the corresponding alkylidine derivatives in situ[XXXIII] followed by treatment of sulfur , the formation of compound 1 proceed via Gwaledreaction[XXXIV] The structure of compound **1** was fully assigned and characterized by different spectroscopic techniques. The IR spectrum showed the expected absorption bands of the NH_2 and NH groups atν_{max}3475, 3328 and 3174cm^{-1} and that of the CO groups at 1695 and 1672 cm^{-1}.The ^{1}H NMR spectrum of **1** showedbroad singlet signal atδ_H5.3 ppm corresponding to the methylinic protons (SCH_2). It also showed the triplet-quartet signal of the ethyl carboxylate functionality at δ_H 1.21 and 4.25ppm.The NH and NH_2 signals appeared at 2.33 and 8.23 ppm, respectively. The EI-MS showed the anticipated molecular ion peak at *m*/*z* 202.

The following mechanism showed the formation of compound **1**

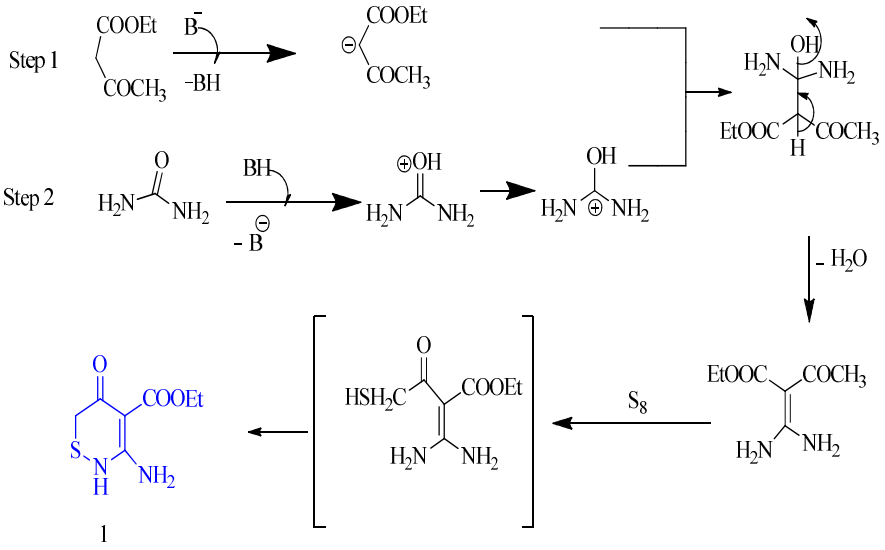
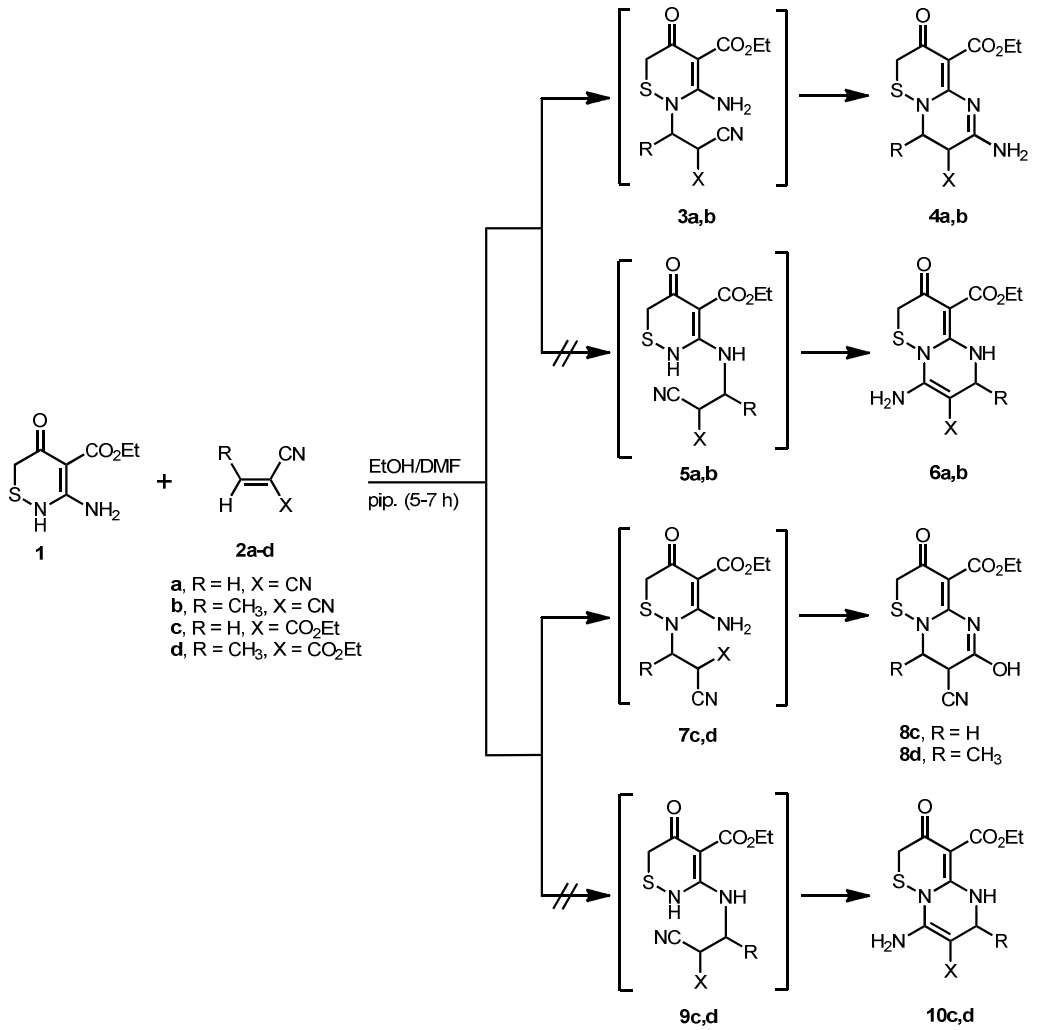


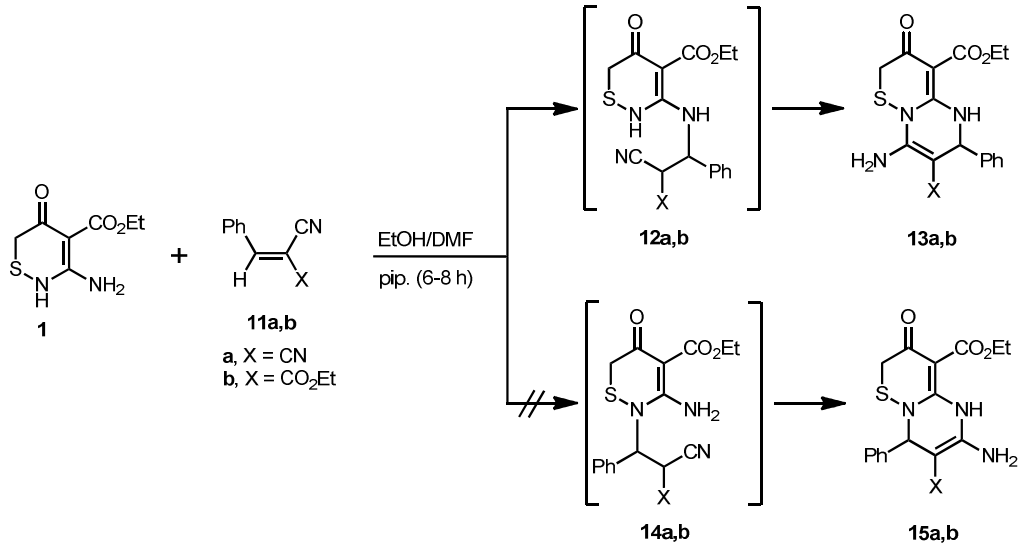
Figure1: Formation of Ethyl 3-amino-5-oxo-5,6-dihydro-2*H*-1,2-thiazine-4-carboxylate **(1)**

Alkylidenemalononitriles**2a-d** were obtained bycondensation of the appropriate aldehydes with active methylene compounds.[XXXV,XXXVI].The amino-functionalized 1,2-thiazine **1**underwent addition with **2a** and **2b**upon refluxing in a mixture of ethanol and dimethyl formamide containing few drops of piperidine to afford the corresponding pyrimido-thiazines**4a**and**4b**, rather than compounds**6a** and**6b** as shown in Scheme**1**.The reactions involved the addition of the NH group of the 1,2-thiazine **1** to the alkylidenemalononitriles double bondthrough intermediates **3a** and**3b**followed by subsequent ring-closure step upon anucleophilicattack of the amino functional group on the electrophilic cyanogroup. As similar, the addition of the1,2-thiazine **1** to the alkylidenemalononitriles**2c**and **2d**were found to proceed *via* intermediates **7c** and **7d**. The cyclization reaction of intermediates **7c** and **7d** includedan intramolecularnucleophilicattack of the amino groups of intermediates **7c** and **7d**on the ethyl carboxylate, rather than the cyanomoiety to yield the fused heterocyclic compounds**8c** and **8d**.The addition reactions of **1**to **2a-d** and the cyclization of intermediates **3a**, **3b**, **7a**, and **7d**were found to be in good agreement with the literature.[35,36] The chemical structures of compounds **4a**, **4b**, **8c**, and **8d** were fully elucidated by using various spectroscopic techniques. The IR spectrum of compound **4a** showed the expected absorption bands of the NH_2, CN and CO moieties at ν_{max}3405, 2215, 1692 and 1672 cm^{-1}. The ^1H NMR spectrum of **4a** showed a singlet signal at δ_H5.22 ppm corresponding to the methylinic protons (SCH_2). It also showed the triplet-quartet signal of the ethyl carboxylate functionality at δ_H1.33 and 4.17 ppm. The NH_2 signal appeared at 8.25 ppm as an abroad singlet. A doublet and multiplet signals appeared at δ_H3.04 and 2.71-2.75 ppm corresponding to the CH_2N and CHCN, respectively. The EI-MS of **4a** showed the expected molecular ionpeak at *m*/*z*280. The characteristic absorption bands in the IR spectrum of compound **4b** appeared at ν_{max} 3412, 2209, 1684 and 1670 cm^{-1}, corresponding to the NH_2, CN and CO functional groups. The ^1H NMR spectrum of **4b** showed the expected signals of the methylinic protons(SCH_2), CHN, CHCN, NH_2 at δ_H 5.18, 3.02-3.06, 2.70, 8.26 ppm, respectively. A triplet -quartet signal appeared at δ_H 1.18-1.23 and 4.09 ppm for the ethyl carboxylate group and the methyl substituent (see experimental section). The molecular ion peak of **4b** appeared in the mass spectrum at *m*/*z* 294. On the other hand, the IR spectrum of compound **8c** showed the expected absorption bandsof the OH, CN and CO moieties at ν_{max}3423, 2216, 1688 and 1665 cm^{-1}. The ^1H NMR spectrum of **8c** showed a singlet signal at δ_H5.21 ppm, corresponding to the methylinic protons (SCH_2). It also showed the triplet-quartet signal of the ethyl carboxylate functionality at δ_H 1.24 and 4.16-4.30 ppm. The OH signal appeared at 2.46 ppm as an abroad singlet. A doublet and multiplet signals appeared at δ_H 3.04 and 2.70-2.78 ppm, corresponding to the CH_2N and CHCN, respectively (see experimental section). The EI-MS of **8c**showed the expected molecular ion peak at *m*/*z* 281.



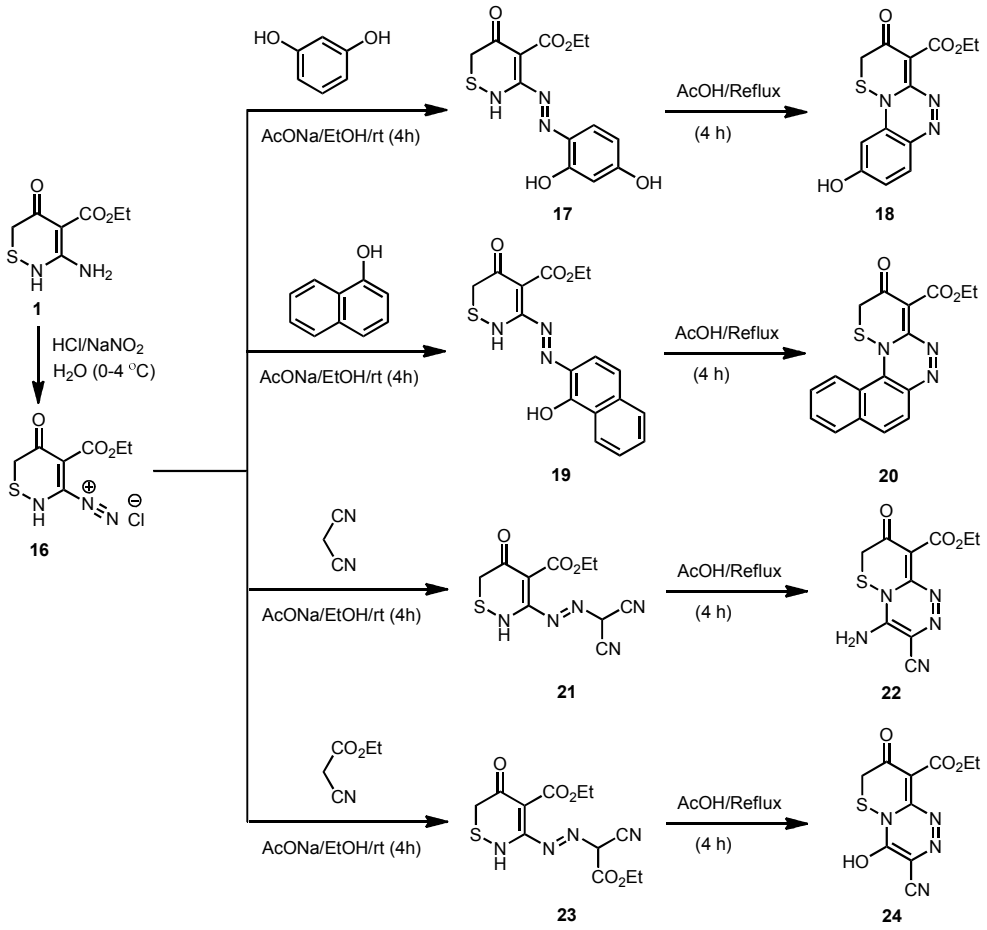
Scheme 1. Synthetic approach to pyrimido[1,2-*b*][1,2]thiazines**4a**, **4b**,**8c**and **8d**.

All the functional groups in **8d** were clearly assigned based on their absorption by IR. The IR spectrum of **8d**showed four characteristic absorption bands at ν_{max} 3423, 2214, 1695 and 1659 cm^{-1}, corresponding to the OH, CN and CO functionalities. The ^1H NMR spectrum of **8d**showed the expected signals of the methylinicprotons (SCH_2), triplet-quartet ester, CHN, CHCN andOH groups at δ_H 5.37, 1.18, 4.20, 3.02, 2.73 and 2.46 ppm, respectively. The molecular ion peak of **8d** appeared in the mass spectrum at *m*/*z* 341. The treatment of the 1,2-thiazine **1** with arylidenemalononitriles**11a** and **11b**yielded the fused pyrimido-thiazine heterocycles**13a** and **13b***via*intermediates **12a** and **12b**, rather than **14a** and **14b**(Scheme 2). This example clearly demonstrates the vital role of the substituent on controlling the regioselectivity of the reaction.[XXXVI]The addition of the amino group of the 1,2-thiazine **1** to form intermediates **12a** and **12b** was followed by an intramolecularnucleophilic addition of the NH functionality on the cyano group. The spectroscopic data were found to be in good agreement with compounds **13a** and **13b**. The IR spectrum of compound **13a** showed the expected absorption bands of the NH_2, NH, CN and CO moieties at ν_{max}3423, 3210, 2199, 1675 and 1648 cm^{-1}.



Scheme 2. Synthetic approach to pyrimido[1,2-*b*][1,2]thiazines**13a** and **13b**.

The ^{1}H NMR spectrum of **13a** showed a singlet signal at δ_H5.42 ppm, corresponding to the methylinic protons (SCH_2). It also showed the triplet-quartet signal of the ethyl carboxylate functionality at δ_H 1.25 and 4.23 ppm. The NH and NH_2 signal appeared at 2.38 and 8.34 ppm, respectively. A singlet signal appeared at δ_H4.46 ppm, corresponding to the CHNH group. The EI-MS of **13a**showed the expected molecular ion peak at *m*/*z*356.The IR spectrum of compound **13b** showed absorption bands at ν_{max}3418, 3199, 1675, 1669 and 1642, corresponding to the NH_2, NH and CO groups. The ^{1}H NMR spectrum of **13b** showed a singlet signal at δ_H5.32 ppm, corresponding to the methylinic protons (SCH_2). It also showed the triplet and quartet signals of the ethyl carboxylate functionality at δ_H 1.24-1.29 and 4.15-4.19 ppm. The NH and NH_2 signal appeared at 2.38 and 8.26 ppm, respectively. A singlet signal appeared at δ_H 4.46 ppm, corresponding to the CHNH group. The EI-MS of **13b**showed the expected molecular ion peak at *m*/*z*403.On the other hand, the synthesis of the thiazino-triazines**18**, **20**, **22** and **24** was achieved through a multiple synthetic pathways, which included diazotization of the primary amino group of **1** to give diazonium salt **16**(Scheme 3).



Scheme 3. Synthetic approach to thiazino-triazines**18**, **20**, **22** and **24**.

The reactions of salt **16** with resorcinol, α-naphthol and active methylene reagents, such as malononitrile and ethyl cyanoacetate in mixtures of ethanolic sodium acetate solutions gave arylazo compounds **17**, **19**, **21** and **23**, which were used without further analysis in the subsequent cyclization steps upon refluxing in acetic acid. The IR spectrum of thiazino-triazine**18** showed the expected absorption bands of the OH and CO moieties at ν_{max}3517, 1702and 1646 cm^{-1}. The ^{1}H NMR spectrums of **18** showed a singlet signal at δ_H5.23 ppm, corresponding to the methylinic protons (SCH_2). It also showed the triplet-quartet signal of the ethyl carboxylate functionality at δ_H1.24 and 4.19ppm. The phenolic OH signal appeared at 8.99 ppm as an abroad singlet. The EI-MS of **18**showed the expected molecular ion peak at *m*/*z*305.

Similarly, the reaction of salt **16** with α-naphtholproceeded through the azo-derivative **19**. The spectroscopic data of the obtained product were in good agreement with compound **20** as shown in Scheme **3**. The characteristic absorption bands of the cyclic ketonic and the exocyclic ester groups appeared at ν_{max}1683 and 1631 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum of **20** showed the methylinic protons (SCH_2) and ester triplet-quartet signals atδ_H 5.10, 1.36 and 4.24, respectively. The molecular ion peak of **20** appeared at *m*/*z* 339.The reaction of malononitrile with **16** resulted inthe formation of **21**, which upon treatment with acetic acid under refluxing conditions yielded **22**.

The cyclization reaction of **21**took place by an attack of the ring NH on the cyano group. The IR spectrum of compound **22** showed the expected characteristic absorption bands of the functionalities existing in the molecule. The IR absorption bands of the CO, CN and

NH_2moieties appeared at ν_{max}1679, 1648, 2218 and 3215 cm^{-1}. The methylinic protons (SCH_2), ester triplet-quartet and NH_2 appeared in the ^1H NMR spectrum of **22 at** 5.06, 1.29 and 4.26 ppm. The mass spectrometry showed the expected molecular ion peak at *m*/*z* 279.As similar to **22**, compound **24** was prepared from **16** and ethyl cyanoacetate through**23**. The ring-closure of **23** was achieved *via* attack of the NH moiety on the ester, rather than the cyano group. The spectroscopic data confirmed the structural framework of **24**. The IR spectrum of compound **24** showed the OH, CO andCN absorption bands atν_{max}3501, 2212, 1675 and 1653 cm^{-1}. The ^1H NMR spectrum of **24** showed the characteristic signals of the methylinic protons (SCH_2) and ester triplet-quartet at 5.21, 1.32 and 4.14 ppm. The OH of **24** was assigned downfield shifted at 11.73 ppm.The mass spectrum showed the molecular ion peak at *m*/*z* 280.

Conclusion

In summary, we have synthesized new pyrimido[1,2-*b*][1,2]thiazines*via* the additionreactions of the amino-functionalized 1,2-thiazine **1** with alkylidene or arylidenemalononitrile derivatives. We also synthesized thiazino[3,2-*c*][1,2,4]triazines from the reactions of the diazo-nium salt of **1** with different phenols and active methylene reagents.

Experimental

All melting points are uncorrected and were measured using an electro thermal IA 9100 apparatus, Shimadzu (Japan). Micro analytical data were performed by using aVario El-Mentar apparatus, Organic Microanalysis Section, MicroanalyticalCenter, Cairo University, Giza, Egypt. The results of the microanalysis were found to be in agreement with the calculated values (± 0.3). The IR spectra (KBr) were recorded on a Perkin-Elmer 1650 spectrophotometer, Micro Analytical Center, Cairo University, Giza, Egypt. $^1H$and ^{13}C NMR spectra were determined on a JEOL 300 MHz in DMSO-d_6, MicroanalyticalCenter, Cairo University, Giza, Egypt. The chemical shifts were expressed in ppm relative to TMS as an internal reference. Mass spectra were recorded on 70 eV EI Ms-QP 1000 EX (Shimadzu, Japan)**,** MicroanalyticalCenter, Cairo University, Giza, Egypt.Compounds**2a-d**, **11a**, and **11b**were prepared according to the reported procedures.[XXXIII,XXXIV]

Ethyl 3-amino-5-oxo-5,6-dihydro-2*H*-1,2-thiazine-4-carboxylate (1)

Ethyl acetoacetate (0.01 mol) and urea (0.01 mol) were mixed in a mixture of ethanol (20 mL) and (5mL) dimethylformamide containing 0.5 mL of piperidine. To this solutionsulfur (0.01 mol) was added andthe reaction mixture was heated under reflux for 8-10 h. The solvent was concentratedand the precipitate was filtered off, washed with methanol and recrystallized from diethyl ether. Yield 53 %; m.p. 135-137°C; IR (KBr): ν_{max}/cm^{-1}=3475, 3328 (NH_2), 3174 (NH), 1695, 1672 (CO); ^1H NMR (DMSO-d_6, ppm): δ_H=1.21 (t, 3H, *J* = 7.50 Hz, $OCH_2\underline{CH_3}$), 2.33 (s, 1H, NH), 4.25 (q, 2H, *J* = 7.20 Hz, $O\underline{CH_2}CH_3$*)*,5.38 (s, 2H, SCH_2), 8.23 (brs, 2H, NH_2). ^{13}C NMR (DMSO-d_6, ppm): δ_C= 14.26, 48.35, 65.12, 88.62, 169.76, 173.33, 179.15; MS, *m*/*z* (%): 202 (M+, 100). Anal.Calcd.for $C_7H_{10}N_2O_3S$ (202); required C, 41.57; H, 4.98; N, 13.85; S, 15.86; found: C, 41.54; H, 5.21; N, 13.88; S, 15.91.

General Procedure for the Synthesis of Compounds (4a, 4b) and (8c, 8d)

A solution of compound (**1**)(0.01 mol) and the corresponding alkylidenemalononitrile (**2a-d)** (0.01 mol) in ethanol (30 mL) was treated with few drops of piperidine. The reaction mixture was refluxed for 5-7 h and the solvent was evaporated *in vacuo*. The remaining solid was triturated with water-ice and acidified with concentratedHCl. The product was collected by filtration and recrystallized from the appropriate solvent to afford compounds **4a**, **4b**, **8c**, and **8d**.

Eth 2-amino-3-cyano-8-oxo-3,4,7,8-tetrahydropyrimido[1,2-*b*][1,2]thiazine-9-carboxylate (4a)

Yield 56 %; m.p. 180-183 °C; IR (KBr): ν_{max}/cm^{-1} = 3405 (NH_2), 2215 (CN), 1692, 1672 (CO); ^{1}H NMR (DMSO-d_6, ppm): δ_H = 1.33 (t, 3H, *J* = 7.10 Hz, CH_3), 2.71-2.75 (d, 1H,CHCN),3.04 (d, 2H, *J* = 4.10 Hz, CH_2N), 4.17 (q, 2H, *J* = 7.11 Hz, O<u>CH_2</u>CH_3),5.22 (s, 2H, SCH_2),8.25 (brs, 2H, NH_2). ^{13}C NMR (DMSO-d_6, ppm): δ_C=14.37, 29.06, 43.12, 51.87, 64.83, 95.34, 117.24, 165.85, 166.97, 173.65, 187.62; MS, *m*/*z* (%): 280 (M+, 46.2). Anal.Calcd.for $C_{11}H_{12}N_4O_3S$ (280.30); required C, 47.13; H, 4.32; N, 19.99; S, 11.44; found: C, 47.08; H, 4.37; N, 20.04; S, 11.39.

Ethyl 2-amino-3-cyano-4-methyl-8-oxo-3,4,7,8-tetrahydropyrimido[1,2-*b*][1,2]thiazine-9-carboxylate (4b)

Yield 61 %; m.p. 275-277°C; IR (KBr): ν_{max}/cm^{-1} =3412 (NH_2), 2209 (CN), 1684, 1670 (CO); ^{1}H NMR (DMSO-d_6, ppm): δ_H= 1.18-1.23 (m, 6H, $2CH_3$), 2.70 (d, 1H, *J* = 3.99 Hz, CHCN), 3.02-3.06 (d, 1H, *J* = 4.10 Hz, CHN), 4.09 (q, 2H, *J* = 7.12 Hz, O<u>CH_2</u>CH_3*)*,5.18 (s, 2H, SCH_2),8.26 (brs, 2H, NH_2). ^{13}C NMR (DMSO-d_6, ppm): δ_C= 14.32, 15.03, 32.11, 43.59, 49.72, 63.99, 106.14, 117.38, 164.29, 166.30, 173.69, 188.23; MS, *m*/*z* (%): 294 (M+, 55). Anal.Calcd.for $C_{12}H_{14}N_4O_3S$ (294.33); required C, 48.97; H, 4.79; N, 19.04; S, 10.89; found: C, 49.02; H, 4.75; N, 18.99; S, 10.92.

Ethyl 3-cyano-2-hydroxy-8-oxo-3,4,7,8-tetrahydropyrimido[1,2-*b*][1,2]thiazine-9-carboxylate (8c)

Yield 85 %; m.p. 270-273°C; IR (KBr): ν_{max}/cm^{-1} =3423 (OH), 2216 (CN), 1688, 1665 (CO); ^{1}H NMR (DMSO-d_6, ppm): δ_H= 1.24 (t, *J* = 7.11 Hz, 3H, CH_3), 2.46 (s, 1H, OH), 2.70-2.78 (t, 1H, CHCN), 3.04 (d, 2H, *J* = 4.13 Hz, CH_2N), 4.16-4.30 (m, 2H,O<u>CH_2</u>CH_3),5.21 (s, 2H, SCH_2). ^{13}C NMR (DMSO-d_6, ppm): δ_C= 14.26, 29.54, 41.36, 50.12, 65.12, 104.52, 115.69, 168.42, 173.53, 177.64, 185.44;MS, *m*/*z* (%): 281 (M+, 73). Anal.Calcd.for $C_{11}H_{11}N_3O_4S$ (281.29); required C, 46.97; H, 3.94; N, 14.94; S, 11.40; found: C, 46.92; H, 3.88; N, 14.89; S, 11.37.

Ethyl 3-cyano-2-hydroxy-4-methyl-8-oxo-3,4,7,8-tetrahydropyrimido[1,2-*b*][1,2]thiazine-9-carboxylate (8d)

Yield 71 %; m.p. 255-257°C; IR (KBr): ν_{max}/cm^{-1} =3423 (OH), 2214 (CN), 1695, 1659 (CO); ^{1}H NMR (DMSO-d_6, ppm): δ_H= 1.18 (t, 3H, *J* = 6.99 Hz, CH_3), 1.31 (s, 3H, CH_3), 2.73 (d, 1H, *J* = 6.08 Hz, CHCN), 2.46 (s,1H,OH), 3.02 (d, 1H, *J* = 4.11 Hz, CHN), 4.20 (q, 2H, *J* = 4.19 Hz,O<u>CH_2</u>CH_3),5.37 (s, 2H, SCH_2).^{13}C NMR (DMSO-d_6, ppm): δ_C=14.22, 15.02, 29.83, 43.62, 49.08, 62.52, 106.74, 117.86, 167.28, 169.54, 176.57, 188.21; MS, *m*/*z* (%): 341 (M+, 65).Anal.Calcd.for $C_{12}H_{13}N_3O_4S$ (295.31); required C, 48.81; H, 4.44; N, 14.23; S, 10.86; found: C, 48.77; H, 4.40; N, 14.03; S, 10.72.

General Procedure for the Synthesis of Compounds 13a and 13b

A solution of (**1**)(0.01 mol) and cinnamonitriles(**11a**)or(**11b)** (0.01 mol) in a mixture of absolute ethanol (20 mL) and DMF (5 mL) was treated with piperidine (0.5 ml). The reaction mixture was refluxed for 6-8h and the solvent was evaporated. The remaining solid product was treated with ice-water and acidified with concentrated HCl. The product was collected by filtration and recrystallized from methanol to afford compounds (**13a**) or (**13b**).

Ethyl 4-amino-3-cyano-8-oxo-2-phenyl-1,2,7,8-tetrahydropyrimido[1,2-*b*][1,2]thiazine-9-ca-rboxylate(13a)

Yield 59 %; m.p. 293-295°C; IR (KBr): ν_{max}/cm^{-1}=3423 (NH_2), 3210 (NH), 2199 (CN), 1675, 1648 (CO); ^{1}H NMR (DMSO-d_6, ppm): δ_H= 1.25 (t, 3H, *J* = 7.0 Hz, CH_3), 2.38 (s,1H,N*H*), 4.46 (s, 1H,NH<u>CH</u>), 4.23 (q, 2H,O<u>CH_2</u>CH_3),5.42 (s, 2H, SCH_2), 7.02-7.23 (m, 5H, CH_{Ar}), 8.34 (brs, 2H, NH_2). ^{13}C NMR (DMSO-d_6, ppm): δ_C= 14.35, 42.98, 51.46, 62.15,

64.36, 85.62, 118.07, 127.25, 127.86, 129.57, 130.28, 133.92, 145.09, 159.86, 166.12, 171.48, 189.07; MS, *m*/*z* (%): 356 (M+, 66). Anal.Calcd.for $C_{17}H_{16}N_4O_3S$ (356.40) required C, 57.29; H, 4.52; N, 15.72; S, 9.00; found: C, 57.23; H, 4.46; N, 15.67; S, 8.97

Diethyl 4-amino-8-oxo-2-phenyl-1,2,7,8-tetrahydropyrimido[1,2-*b*][1,2]thiazine-3,9-dicarboxylate (13b)

Yield 57 %; m.p. 240-242°C; IR (KBr): ν_{max}/cm^{-1}= 3418 (NH_2), 3199 (NH), 1675, 1669, 1642 (CO); ^{1}H NMR (DMSO-d_6, ppm): δ_H= 1.24-1.29 (t, 6H, $2CH_3$), 2.38 (s, 1H, NH), 4.15-4.19 (q, 4H,2O$\underline{CH_2}CH_3$), 4.46 (s, 1H,NH$\underline{CH}$),5.32 (s, 2H, SCH_2), 6.92-7.0 (m, 5H, CH_{Ar}), 8.26 (brs, 2H, NH_2). ^{13}C NMR (DMSO-d_6, ppm): δ_C= 14.32, 14.68, 43.05, 49.42, 62.98, 63.11, 83.90, 85.54, 125.83, 127.65, 127.98, 129.38, 130.76, 143.68, 149.29, 164.48, 167.35, 168.04, 188.85; MS, *m*/*z* (%): 403 (M+, 83).Anal. Calcd.for $C_{19}H_{21}N_3O_5S$ (403.45) required C, 56.56; H, 5.25; N, 10.42; S, 7.95 found: C, 56.60; H, 5.21; N, 10.38; S, 8.00.

General Procedure for the Reaction of Diazotized (1) with Active Methylene Compounds

A solution of diazotized (**1**)(0.01 mol) was added dropwise with stirring at 0-5 ℃ over a course of 30 minutes to a cold solution of resorcinol, α-naphthol, malononitrileor ethyl cyanoacetate in ethanol (50 mL) containing 5 g of sodium acetate. The reaction mixture was stirred for further 4 h, then kept in an ice chest for additional 12 hand finally diluted with water. The precipitated solid was collected by filtration, washed with water, dried and recrystallized from methanol to afford the corresponding arylazocompounds(**17**),(**19**),(**21**) and(**23**) and the products were used in following steps without further analysis**.**

General Procedure for the Cyclization of Compound (17),(19),(21) and (23)

A solution of compounds (**17**),(**19**),(**21**) or(**23**) (0.00327 mol) in acetic acid (30 mL) was refluxed for 4 h. The solvent was concentrated *invacuo*and the solid precipitate was filtered off, washed with water and dried. The crude product was recrystallized from ethanol to afford the corresponding fused ring systems (**18**), (**20**),(**22**)or(**24**).

Ethyl 9-hydroxy-3-oxo-2,3-dihydrobenzo[*e*][1,2]thiazino[3,2-*c*][1,2,4]triazine-4-carboxylate (18)

Yield 75 %; m.p. 225-227°C; IR (KBr): ν_{max}/cm^{-1}= 3517 (OH), 1702, 1646 (CO); ^{1}H NMR (DMSO-d_6, ppm): δ_H= 1.24 (t, 3H, *J* = 7.02 Hz, CH_3), 4.19 (q, 2H, *J* = 7.21 Hz, O$\underline{CH_2}CH_3$*)*,5.23 (s, 2H, SCH_2), 7.05-7.01 (m, 3H, CH_{Ar}), 8.99 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, ppm): δ_C= 14.24, 42.51, 64.33, 106.12, 110.34, 112.52, 124.67, 133.02, 147.21. 156.17, 162.57, 166.63, 189.03;MS, *m*/*z* (%): 305 (M+, 100). Anal.Calcd.for $C_{13}H_{11}N_3O_4S$ (305.31) required C, 51.14; H, 3.63; N, 13.76; S, 10.50 found: C, 51.18; H, 3.66; N, 10.76; S, 10.46.

Ethyl 3-oxo-2,3-dihydronaphtho[1,2-*e*][1,2]thiazino[3,2-*c*][1,2,4]triazine-4-carboxylate (20)

Yield 61 %; m.p. 286-289°C; IR (KBr): ν_{max}/cm^{-1}= 1683, 1631 (CO); ^{1}H NMR (DMSO-d_6, ppm): δ_H= 1.36 (t, 3H, *J* = 7.11 Hz, CH_3), 4.24 (q, 2H, *J* = 7.19 Hz, O$\underline{CH_2}CH_3$),5.10 (s, 2H, SCH_2), 7.44-7.84 (m, 6H, CH_{Ar}). ^{13}C NMR (DMSO-d_6, ppm): δ_C= 14.43, 43.35, 65.04, 112.86, 114.72, 121.08, 122.14, 125.36, 126.26, 127.91, 130.11, 132.26, 133.54, 146.74, 159.36, 166.25, 187.89; MS, *m*/*z* (%): 339 (M+, 100).Anal. Calcd.for $C_{17}H_{13}N_3O_3S$ (339.37) required C, 60.17; H, 3.86; N, 12.38; S, 9.45 found: C, 51.08; H, 3.72; N, 10.81; S, 10.44.

Ethyl 4-amino-3-cyano-8-oxo-7,8-dihydro-[1,2]thiazino[3,2-*c*][1,2,4]triazine-9-carboxylate (22)

Yield 65 %; m.p. 262-264°C; IR (KBr): ν_{max}/cm^{-1}= 3215 (NH_2), 2218 (CN), 1679, 1648 (CO); ^{1}H NMR (DMSO-d_6, ppm): δ_H= 1.29 (t, 3H, *J* = 7.06 Hz, CH_3), 4.26 (q, 2H, *J* = 7.16 Hz, O$\underline{CH_2}CH_3$*)*,5.06 (s, 2H, SCH_2), 9.45 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, ppm): δ_C= 14.35, 43.86, 53.42, 63.20, 115.81, 118.08, 147.38, 167.37, 176.50, 187.91;MS, *m*/*z* (%): 279

(M+, 100).Anal. Calcd.for $C_{10}H_9N_5O_3S$ (279.28) required C, 43.01; H, 3.25; N, 25.08; S, 11.48 found: C, 42.96; H, 3.30; N, 25.11; S, 11.43.

Ethyl 3-cyano-4-hydroxy-8-oxo-7,8-dihydro-[1,2]thiazino[3,2-*c*][1,2,4]triazine-9-carboxylate (24)

Yield 63 %; m.p. 252-255°C; IR (KBr): ν_{max}/cm^{-1}=3501 (OH), 2212 (CN), 1675, 1653 (CO); ^{1}H NMR (DMSO-d_6, ppm): δ_H= 1.32 (t, 3H, J = 7.00 Hz, CH_3), 4.14 (q, 2H, J = 7.24 Hz, O$\underline{CH_2}$CH$_3$*)*,5.21 (s, 2H, SCH_2), 11.73 (brs, 1H, OH). ^{13}C NMR (DMSO-d_6, ppm): δ_C= 14.22, 44.51, 46.03, 65.43, 116.07, 121.40, 148.26, 165.19, 188.12, 190.72;MS, *m*/*z* (%): 280 (M+, 75).Anal. Calcd.for $C_{10}H_8N_4O_4S$ (280.26) required C, 42.86; H, 2.88; N, 19.99; S, 11.44 found: C, 42.82; H, 2.85; N, 20.03; S, 11.42.

References

[I] http://www.who.int/mediacentre/factsheets/fs104/en/

[II] http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/

[III] S. M.Sayed, M.A. Khalil, M.A.Raslan, *Am. J. Org. Chem*., 2(6): 151-160.

[IV] M. Hegab, N. Yousef, H. Nour, M. Ellithey, M. Arbid, *Acta. Pharm.*, **2008**, *58*, 15.

[V] M.-G. Kim, S.-E.Lee, J.-Y.Yang, H.-S.Lee, *J. Sci. Food Agric*., **2014**, *94*, 2529.

[VI] B. Tozkoparan, G. Aktay, E. Yeşilada, *Farmaco*, **2002**, 57(2):145-52.

[VII] A. Pearce, E. Chia, M. Berridge, G. Clark, J. Harper, L. Larsen, E. Maas,M. Page,N. Perry, V. Webb,B. Copp, *J. Nat. Prod.*, **2007**, *70*, 936.

[VIII] D. Bózsing, P. Sohár, G. Gigler, G. Kovács, European Journal of Medicinal Chemistry, **1996**, 31(9), 663.

[IX] M. Rinaldi, P. Pecorari, L. Costantino, A. Provvisionato, M. Malagoli, C. Cermelli, *Farmaco*, **1992**, 47, 1315.

[X] R. Gupta, R.P.Chaudhary, *Phosphorus Sulfur and Silicon and the Relat. Elem.*, **2012**, *187*, 6, 735.

[XI] N. Ingarsal, P. Amutha, S. Nagarajan, *J. Sulfur Chem.*, **2006**, 27(5), 455.

[XII] N. Edayadulla, P. Ramesh, *Eur. J. Med. Chem.*, **2015**, *106*, 44.

[XIII] L.-Q. Zhang, L.-P.Guan, C.-X.Wei, X.-Q.Deng, Z.-S.Quan, *Chem. Pharm. Bull.*, **2010**, *58*, 326.

[XIV] N. Edayadulla, P. Ramesh, *Eur. J. Med. Chem.*, **2015**, *106*, 44.

[XV] J. Park, S. Rhee, N. Kang, W. Jung, H. Kim, J. Kim, S. Kang, H. Cheon, J. Ahn, K. Kim, *Biochem. Pharmacol.*,**2011**, *81*, 1028.

[XVI] X. Chen, S. Zhang, Y. Yang, S. Hussain, M. He, D. Gui, B. Ma, C. Jing, Z. Qiao, C. Zhu, Q. Yu., *Bioorg. Med. Chem.*, **2011**, *19*, 7262.

[XVII] X. Chen, C. Zhu, F. Guo, X. Qiu, Y. Yang, S. Zhang, M. He, S. Parveen, C. Jing, Y. Li, B. Ma, *J. Med. Chem*.,**2010**, 53(23):8330.

[XVIII] H.-M. Wu, K. Zhou, T. Wu, Y. Cao, *Chem. Biol. Drug Des.*,**2016**, *88*, 411.

[XIX] M. Rinaldi, P. Pecorari, L. Costantino, A. Provvisionato, M. Malagoli, C. Cermelli, *Farmaco*., **1992**, *47*, 1315.

[XX] C. Asquith, M. Meli, L. Konstantinova, T. Laitinen, M. Peräkylä, A. Poso, O. Rakitin, K. Allenspach, R. Hofmann-Lehmann, S. Hilton, *Bioorg. Med. Chem. Lett.*, **2014**, *24*, 2640.

[XXI] W. Malinka, M. Kaczmarz, A. Redzicka, *Acta Pol. Pharm.*, **2004**, *61*, 100.

[XXII] B. Morak-Młodawska, K. Pluta, M. Latocha. M. Jeleń, *Med. Chem. Res*., **2016**, *25*, 2425.

[XXIII] M. Ferreira, L. Assunção, F. Filippin-Monteiro, T. Creczynski-Pasa, M. Sá, *Eur. J. Med. Chem.*, **2013**, *70*, 411.
[XXIV] B. Tozkoparan, G. Aktay, E. Yeşilada, *Farmaco*, **2002**, *57*, 145.
[XXV] E. Lee, S. Kwon, S. Kim, *Arch. Pharm. Res.*, **1999**, *22*, 44.
[XXVI] S.K. Kwon, M.-S. Park**,** *Arch. Pharm. Res*., **1992**, 15(3), 251.
[XXVII] T. El Malah, H. Nour, A. Nayl, R. Elkhashab, F. Abdel-Megeid, M. Ali,*Aust. J. Chem.*, **2016**, *69*, 905.
[XXVIII] P. Singla, V. Luxami, K. Paul, *Bioorg. Med. Chem.*, **2015**, *23*, 1691.
[XXIX] S. Manohar, S. I. Khan, D. S. Rawat, *Chem. Biol. Drug Des.*,**2011**, *78*, 124.
[XXX] A. Solankee, K. Kapadia, A. C`iric´, M. Sokovic´, I. Doytchinova, A. Geronikaki, *Eur. J. Med. Chem.*, **2010**, *45*, 510.
[XXXI] R. Kumar, M. S. Yar, S. Chaturvedi, A. Srivastava, *Int. J. Pharm. Tech.Res.*, **2013**, *5*, 1844.
[XXXII] S. Kim, R. Kubec, R. Musah, *J. Ethnopharmacol.*, **2006**, *104*, 188.
[XXXIII] A. K. Khalafallah, R. M. Abd El-Aal and N. A. A. El Kanzi,*J. Chin. Chem. Soc., **2002**, 49, No. 3,* 387-396.
[XXXIV] Gewald, K. Angew. Chem. **1961**, 73, 114 .
[XXXV] A. K.Khalafaliah, R.M.AbdEl-Aal, N.A.A. El Kanzi*, Heterocycl. Commun.*,**2002**, *8*,397.
[XXXVI] M. A. Raslan, R. M. Abd El-Aal, M. E. Hassan, N. A. Ahamed ,K. U. Sadek,*J.Chin. Chem. Soc.*, **2001**, *48*, 91.

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