

HETEROCYCLES, Vol. 96, No. 11, 2018, pp. 1897 - 1909. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 9th August, 2018, Accepted, 25th October, 2018, Published online, 15th November, 2018
DOI: 10.3987/COM-18-13969

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF SOME NOVEL FUSED PYRIMIDO[1,2-*b*][1,2,4]-TRIAZINE, TRIAZINO[2,3-*a*]QUINAZOLINE AND IMIDAZO[1,2-*b*]-[1,2,4]TRIAZINE DERIVATIVES

Khaled S. Mohamed^{1*} and Elsherbiny H. El-Sayed²

¹Engineering Chemistry Department, Higher Institute for Engineering and Technology, New Damietta, Egypt. E-mail: Khaled_samirm@yahoo.com

²Department of Chemistry, Faculty of Science, Port Said University, 42526 Port Said, Egypt. E-mail: Saeed201691@yahoo.com

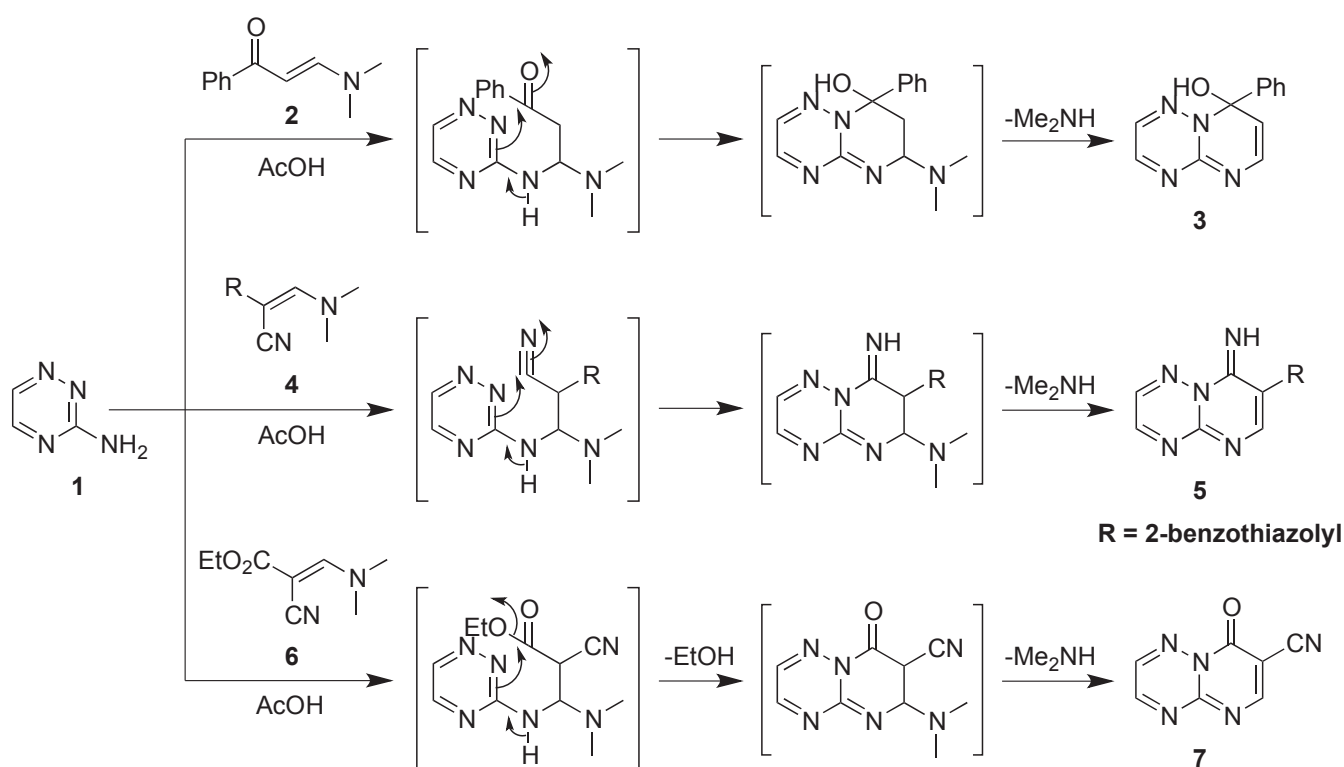
Abstract – A novel pyrimido[1,2-*b*][1,2,4]triazine derivatives were synthesized by allowing 3-amino-1,2,4-triazine (**1**) to react with different reagents such as enamionone, enamionitriles, 3-bromopropanenitrile, 2-(2,5-dimethoxybenzylidene)malononitrile and 1,3-dicarbonyl compounds. Moreover, triazino[2,3-*a*]quinazoline derivatives were synthesized by reaction of **1** with 2-((dimethylamino)methylene)-5,5-dimethylcyclohexane-1,3-dione (**18**) and 2,6-bis(pyridin-3-ylmethylene)cyclohexan-1-one (**20**). On the other hand, treatment of **1** with 2-bromo-1-(naphtho[2,1-*b*]furan-2-yl)ethan-1-one (**22**) afforded imidazo[1,2-*b*][1,2,4]triazine derivative (**23**). The newly synthesized compounds were evaluated for their antimicrobial activities based on inhibition diameter zone against Gram positive and Gram negative bacteria.

INTRODUCTION

1,2,4-Triazine platform is a protuberant structural core moiety present in numerous biologically active compounds, such as antibacterial,^{1,2} antifungal,^{3,4} antimalarial,⁵ antiinflammatory,⁶ anticonvulsant,⁷ neuroprotective properties,⁸ anticancer,⁹ and anti-HIV.^{10,11} Also, some fused 1,2,4-triazine derivatives as imidazo[2,1-*c*][1,2,4]triazine derivatives have been found to reveal potent anticancer activities.¹²⁻¹⁴ By taking the above features into consideration, here we aim to synthesize pyrimido[1,2-*b*][1,2,4]triazine, triazino[2,3-*a*]quinazoline, and imidazo[1,2-*b*][1,2,4]triazine derivatives and evaluate their activity against Gram positive and Gram negative bacteria.

RESULTS AND DISCUSSION

The target compounds pyrimido[1,2-*b*][1,2,4]triazine derivatives were synthesized starting from 3-amino-1,2,4-triazine (**1**) as shown in Schemes 1-3. A new synthetic approach for construction pyrimidine nucleus fused to 1,2,4-triazine moiety in compound **1** based on the treatment of **1** with enaminone **2** or enaminonitriles **4**¹⁵ and **6** in glacial acetic acid furnished 8-phenyl-8*H*-pyrimido[1,2-*b*][1,2,4]triazin-8-ol (**3**), 7-(2-benzothiazolyl)-8*H*-pyrimido[1,2-*b*][1,2,4]triazin-8-imine (**5**) and 8-oxo-8*H*-pyrimido[1,2-*b*][1,2,4]triazine-7-carbonitrile (**7**), respectively (Scheme 1).¹⁶

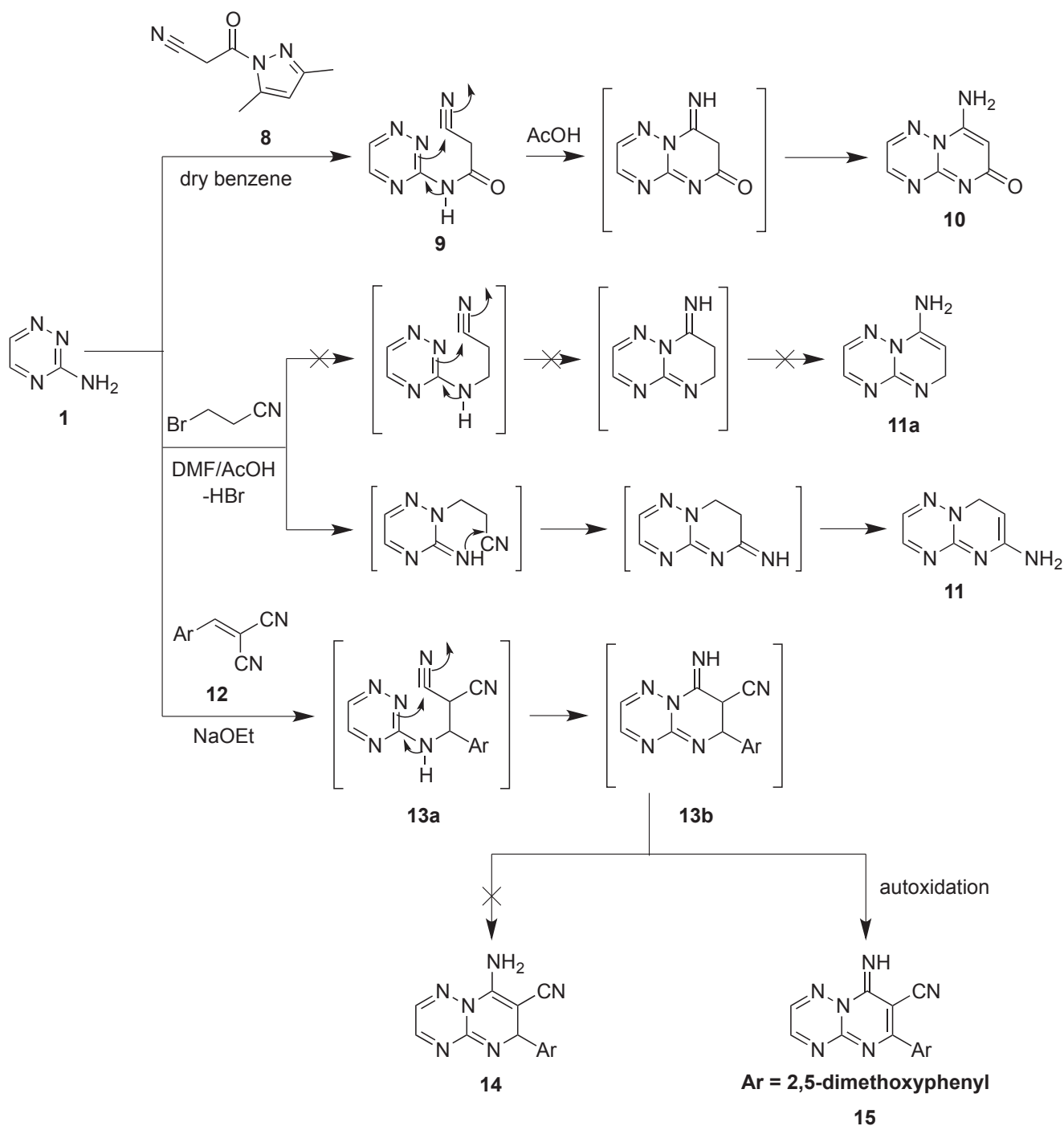


Scheme 1

Formation of fused pyrimidine ring to 1,2,4-triazine could be occurred through C₃-N₂ or C₃-N₄ in compound **1**. X-Ray study of compound **1** confirmed that the double bond character is present between C₃-N₂ and not between C₃-N₄,¹⁷ in triazine ring that support formation of pyrimido[1,2-*b*][1,2,4]triazine derivatives and not pyrimido[2,1-*c*][1,2,4]triazine derivatives. The mechanism of formation of compounds **3**, **5** and **7** was depicted in Scheme 1. The assignment of structures **3**, **5** and **7** were based on analytical and spectroscopic data. Their mass spectra provided molecular ion peaks coincide with the molecular weight of proposed structures of **3**, **5** and **7**. ¹H NMR spectrum of **3** exhibited singlet signal at δ 4.61 ppm (D₂O-exchangable) due to OH group, in addition to four doublet signals at δ 6.84, 7.78, 8.31 and 8.65 ppm attributable to C₇-H, C₆-H, C₃-H and C₂-H, respectively. ¹H NMR of **7** devoid the

triplet-quartet pattern due to ethoxy group, which confirm that it was involved in cyclocondensation reaction.

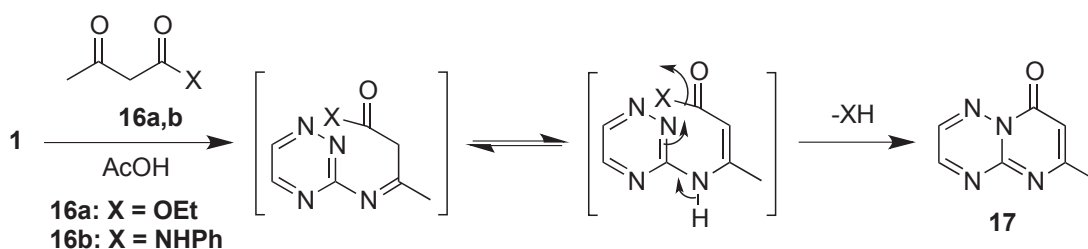
A novel approach for the synthesis of pyrimido[1,2-*b*][1,2,4]triazine derivatives was achieved by reaction of compound **1** with different nitrile derivatives (Scheme 2). Thus, cyanoacetylation of compound **1** with 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (**8**) in refluxing benzene afforded 2-cyano-*N*-(1,2,4-triazin-3-yl)acetamide (**9**).¹⁸ The structure of **9** was supported based on its elemental analysis and



Scheme 2

spectral data. The IR spectrum of **9** presented three absorption bands at 3421, 2197 and 1691 due to NH, CN and C=O groups, respectively. Its ^{13}C NMR revealed three signals at δ 26.2, 117.3 and 168.8 ppm assignable for CH_2 , CN and C=O groups, respectively. When compound **9** was refluxed in glacial AcOH, it underwent an intermolecular nucleophilic cycloaddition reaction to afford 8-amino-6*H*-pyrimido[1,2-*b*][1,2,4]triazin-6-one (**10**). Absence of any stretching frequencies in the region 2100-2250 cm^{-1} in the IR spectrum of compound **10** confirmed that cyano group was involved in the cyclization reaction. Moreover, its ^1H NMR displayed two singlet signals at δ 6.42 and 6.66 ppm attributable to CH and NH_2 protons, respectively. On the other hand, interaction of **1** with 3-bromopropanenitrile in refluxing DMF/AcOH can proceed in two mechanistic routes to afforded either isomeric structure **11a** or **11** (Scheme 2). Reported literature¹⁹ showed that reaction of 2-aminoazines with halogenated electrophiles with other function center occur firstly by nucleophilic substitution through the endocyclic N at first followed by cyclization *via* exocyclic NH, which support formation of 8*H*-pyrimido[1,2-*b*][1,2,4]triazin-6-amine (**11**). Its structure was proved by its spectral data. Thus, ^1H NMR displayed doublet signal at δ 4.13 ppm due to CH_2 protons and triplet signal at δ 5.69 ppm attributable to $\text{C}_7\text{-H}$ in addition to singlet signal (D_2O exchangeable) at δ 6.65 ppm assignable for NH_2 protons. Moreover, for the synthesis of more pyrimido[1,2-*b*][1,2,4]triazine derivatives, compound **1** was refluxed with 2-(2,5-dimethoxybenzylidene)-malononitrile (**12**) in the presence of NaOEt to afford 6-(2,5-dimethoxyphenyl)-8-imino-8*H*-pyrimido[1,2-*b*][1,2,4]triazine-7-carbonitrile (**15**) instead of the expected product **14**. The formation of **15** was proceeded *via* aza-Michael reaction of amino group to **12** forming the intermediate **13a** that undergo an intermolecular nucleophilic cycloaddition reaction to afford the intermediate **13b**. Autoxidation of **13b** gave the final isolable product **15**. The ^1H NMR substantiated the structure of **15** where it displayed only two singlet signals in the aliphatic region at δ 3.71 and 3.79 ppm due to two methoxy groups and no other signals for $\text{C}_6\text{-H}$ proton in structure **14**.

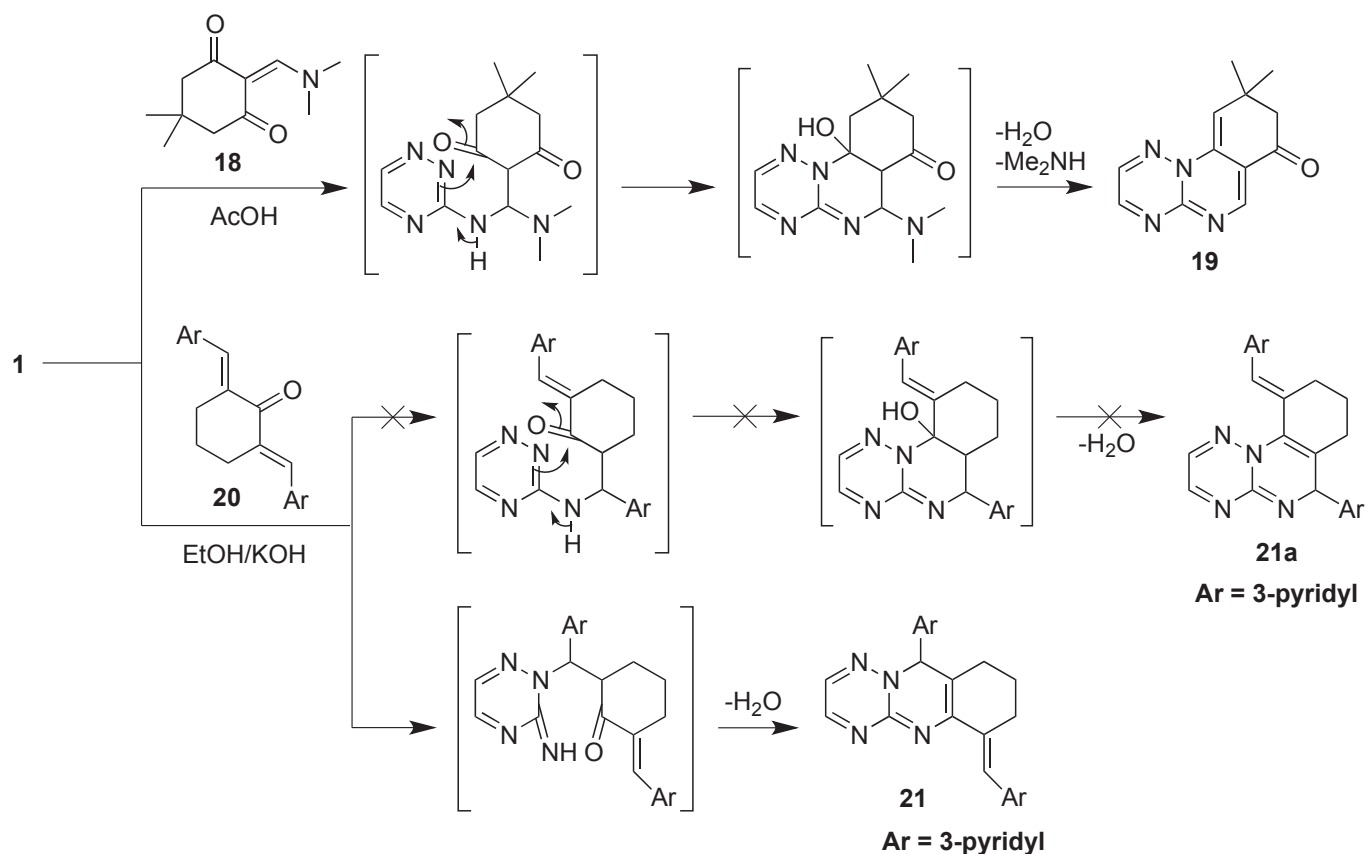
Cyclocondensation reaction of **1** with either of ethyl acetoacetate (**16a**)²⁰ or acetoacetanilide (**16b**) in refluxing glacial AcOH gave the same product namely 6-methyl-8*H*-pyrimido[1,2-*b*][1,2,4]triazin-8-one (**17**) (Scheme 3). The structure of **17** was deduced from its elemental and spectral data. Its mass spectrum revealed molecular ion peak at m/z 162 which is equivalent to molecular mass of proposed structure. In



Scheme 3

addition, its ^1H NMR displayed two singlet signals at δ 2.32 and 6.56 ppm due to CH_3 and $\text{C}_7\text{-H}$, respectively.

With the abovementioned results taken into consideration and the mechanistic behavior of **1**, the synthesis of substituted triazino[2,3-*a*]quinazoline **19** and **21** was proceeded *via* the reaction of **1** with enaminone **18**²¹ and 2,6-bis(pyridin-3-ylmethylene)cyclohexan-1-one (**20**), respectively (Scheme 4).



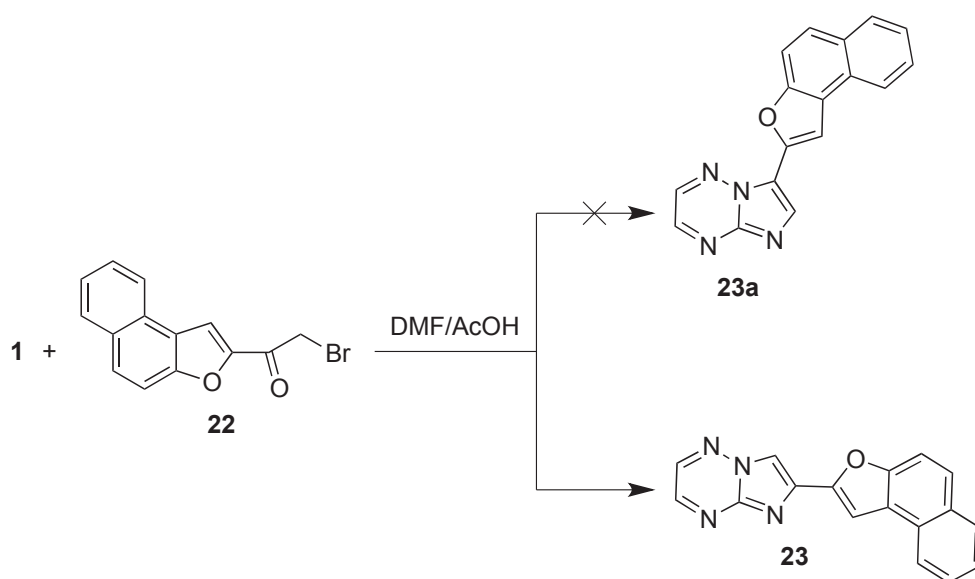
Scheme 4

Treatment of **1** with α,β -unsaturated ketone can lead to two isomeric products **21a** or **21**. According to the reported literature,²⁰ the reaction of **1** with α,β -unsaturated carbonyl compound occur *via* aza-Michael reaction of *N*-2 in triazine ring followed by cyclocondensation, which would suggest the formation of isomeric structure **21** than **21a** (Scheme 4).

The structure of compounds **19** and **21** was deduced from elemental analysis and spectral data, whereas the molecular weights of structures **19** and **21** were identical with obtained from mass spectroscopy. The ^1H NMR spectrum of **19** displayed five singlet signals at δ 1.18, 1.22, 2.43, 5.65 and 8.93 ppm due to two methyl groups, CH_2 , $\text{C}_{10}\text{-H}$ and $\text{C}_6\text{-H}$, respectively. The ^{13}C NMR of **21** exhibited four signals at δ 26.4, 28.6, 31.2 and 64.2 ppm attributable to three CH_2 and $\text{C}_6\text{-H}$, respectively.

Reported literatures of interaction of **1** with α -haloketone indicated possibility of formation imidazo[2,1-*c*][1,2,4]triazine derivatives²² or imidazo[1,2-*b*][1,2,4]triazine derivatives.¹⁹ Herein, we report that treatment of **1** with 2-bromo-1-(naphtho[2,1-*b*]furan-2-yl)ethan-1-one afforded 6-(naphtho[2,1-*b*]furan-2-yl)imidazo[1,2-*b*][1,2,4]triazine (**23**) based on the reported X-ray study of imidazo [1,2,4]triazine²³ (Scheme 5).

Reaction of **1** with α -haloketone can lead to 6-substituted imidazo[1,2-*b*][1,2,4]triazine or 7-substituted imidazo[1,2-*b*][1,2,4]triazine. A careful literature survey revealed the formation of 6-substituted imidazo[1,2-*b*][1,2,4]triazine instead of 7-substituted isomer.^{19,22,24,25}



Scheme 5

The structure of **23** was elucidated based on its IR spectrum, ¹H NMR, ¹³C NMR and mass spectrum.

ANTIMICROBIAL ASSAY

The antibacterial activity of newly synthesized compounds under investigation was evaluated *in vitro* against *Staphylococcus aureus* and *Staphylococcus epidermidis* as examples of Gram-positive bacteria and *Escherichia coli* and *Proteus mirabilis* as examples of Gram-negative bacteria using filter paper disc diffusion method.²⁶ Ciprofloxacin was used as a control standard for *in vitro* antibacterial activity. Antibacterial activity was expressed as inhibition diameter zones in millimeters (mm) of novel obtained products as in Table 1.

Table 1. Inhibition diameter zone (mm) of the newly synthesized compounds

Compound No.	Inhibition zone diameter (mm) of bacteria			
	Gram (+) bacteria		Gram (-) bacteria	
	<i>S. aureus</i>	<i>S. epidermidis</i>	<i>P. mirabilis</i>	<i>E. coli</i>
3	NA	NA	NA	NA
5	21.62±0.33	22.65±0.31	19.93±0.04	19.02±0.02
7	19.52±0.36	18.26±0.07	17.42±0.02	16.10±0.02
9	20.50±0.18	20.19±0.07	18.53±0.43	18.02±0.21
10	NA	NA	NA	NA
11	NA	NA	NA	NA
15	20.61±0.03	19.64±0.10	16.96±0.15	16.56±0.03
17	NA	NA	NA	NA
19	16.46±0.18	15.72±0.10	17.73±0.02	19.36±0.03
21	18.52±0.02	18.72±0.04	19.63±0.09	18.56±0.01
23	14.22±0.13	13.88±0.10	15.76±0.03	12.26±0.03
Ciprofloxacin	21.46±0.31	22.64±0.54	22.24±0.30	23.82±0.47

"NA": No Activity

As shown in Table 1, compounds **3**, **10**, **11** and **17** are biologically inactive against the tested Gram positive and Gram negative bacteria. Compound **5** gave an outstanding result especially towards Gram positive bacteria. In addition, compounds **7**, **9** and **15** provided strong biological activity against Gram positive bacteria than Gram negative bacteria. Other tested compounds gave moderate results.

STRUCTURE-ACTIVITY RELATIONSHIP STUDIES

Structure activity relationship for pyrimido[1,2-*b*][1,2,4]triazine derivatives **3**, **5**, **7**, **10**, **11**, **15** and **17** showed clearly that absence of substituent in C₇ in pyrimido[1,2-*b*][1,2,4]triazine skeleton make it biologically inactive as in compounds **3**, **10**, **11** and **17**. Introducing of electron withdrawing group such as cyano group (compounds **7**, **9** and **15**) or 2-benzothiazolyl group (compound **5**) led to strong activity especially towards Gram positive bacteria. The best result was obtained from compound **5** and this may be attributed to presence of benzothiazole moiety.²⁷ [1,2,4]-Triazino[2,3-*a*]quinazoline derivatives **19** and **21** showed moderate to strong activity,²⁸ compound **21** gave more activity than produced by **19** and this is may be due to presence of electron deficient 3-pyridyl ring substituent.^{29,30}

CONCLUSION

The present study describes the synthesis and investigates the antimicrobial activities of fused heterocyclic compounds containing 1,2,4-triazine moiety with the hope of discovering new structure leads serving as antimicrobial agents.

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus are uncorrected. IR spectra were recorded KBr disc on a Mattson 5000 FTIR spectrophotometer at Microanalytical Unit, Faculty of Science, Mansoura University. The ^1H NMR and ^{13}C NMR spectra were measured on Bruker 400 (100 MHz) in $\text{DMSO-}d_6$ as solvent, using tetramethylsilane (TMS) as an internal standard, and chemical shifts are expressed as δ_{ppm} . Mass spectra were determined on Finnigan Incos 500 (70 eV). Elemental analyses were carried out at the Microanalytical Centre, Faculty of Science, Cairo University, Egypt. All the compounds were checked for their purity on TLC (silica gel, aluminium sheets).

General procedure for the synthesis of 8*H*-pyrimido[1,2-*b*][1,2,4]triazine derivatives 3, 5 and 7.

To a solution of compound 1 (0.96 g, 0.01 mol), in glacial acetic acid (20 mL), 3-(dimethylamino)-1-phenylprop-2-en-1-one (2) (1.75 g, 0.01 mol), 2-(benzo[*d*]thiazol-2-yl)-3-(dimethylamino)acrylonitrile (4) (2.29 g, 0.01 mol) or ethyl 2-cyano-3-(dimethylamino)acrylate (6) (1.68 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 8-10 h (the reaction progress was monitored by TLC). Upon completion, the reaction mixture was allowed to cool and triturated with EtOH. The obtained solid product was collected by filtration, dried and recrystallized from EtOH to give compounds 3, 5 and 7.

8-Phenyl-8*H*-pyrimido[1,2-*b*][1,2,4]triazin-8-ol (3)

Yellow powder; yield (87%); mp 183-185 °C (EtOH); IR (KBr): $\nu_{\text{max}}/\text{cm}^{-1} = 3418$ (OH), 1646 (C=N); ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ (ppm): 4.61 (s, 1H, OH), 6.84 (d, $J = 10.2$ Hz, 1H, C₇-H), 7.21-7.62 (m, 5H, Ar-H), 7.78 (d, $J = 10.4$ Hz, 1H, C₆-H), 8.31 (d, $J = 2.0$ Hz, 1H, C₃-H), 8.65 (d, $J = 2.2$ Hz, 1H, C₂-H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ (ppm): 90.5, 126.0, 127.2, 128.6, 129.8, 130.7, 140.1, 144.2, 150.2, 158.5; MS m/z (%): 226 (M^+ , 33.0); Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}$ (226.24) C, 63.71; H, 4.46; N, 24.76%. Found: C, 63.68; H, 4.48; N, 24.69%.

7-(2-Benzothiazolyl)-8*H*-pyrimido[1,2-*b*][1,2,4]triazin-8-imine (5)

Yellowish brown powder; yield (82%); mp 296-298 °C (EtOH); IR (KBr): $\nu_{\text{max}}/\text{cm}^{-1} = 3320$ (NH), 1646 (C=N); ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ (ppm): 7.42-7.45 (m, 2H, Ar-H), 8.21-8.25 (m, 2H, Ar-H), 8.32 (d, $J = 2.2$ Hz, 1H, C₃-H), 8.41 (s, 1H, C₆-H), 8.64 (d, $J = 2.2$ Hz, 1H, C₂-H), 9.86 (s, 1H, NH); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ (ppm): 121.3, 123.6, 124.5, 126.2, 130.7, 136.4, 140.3, 143.2, 150.5, 152.2, 158.5, 160.3, 162.1; MS m/z (%): 280 (M^+ , 18.6); Anal. Calcd for $\text{C}_{13}\text{H}_8\text{N}_6\text{S}$ (280.31): C, 55.70; H, 2.88;

N, 29.98%. Found: C, 55.79; H, 2.91; N, 30.04%.

8-Oxo-8*H*-pyrimido[1,2-*b*][1,2,4]triazine-7-carbonitrile (7)

Yellowish brown powder; yield (75%); mp 268-270 °C (EtOH); IR (KBr): $\nu_{\max}/\text{cm}^{-1} = 2215$ (CN), 1678 (C=O), 1648 (C=N); ^1H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.30 (d, $J = 2.2$ Hz, 1H, C₃-H), 8.65 (d, $J = 2.2$ Hz, 1H, C₂-H), 8.87 (s, 1H, C₆-H); ^{13}C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 98.5, 116.8, 140.4, 150.6, 158.3, 160.2, 168.7; MS m/z (%): 173 (M⁺, 48.0); Anal. Calcd for C₇H₃N₅O (173.14): C, 48.56; H, 1.75; N, 40.45%. Found: C, 48.60; H, 1.80; N, 40.53%.

Synthesis of 2-cyano-*N*-(1,2,4-triazin-3-yl)acetamide (9)

To a solution of compound **1** (0.96 g, 0.01 mol) in dry benzene (15 mL), 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (**8**) (1.63 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 5 h. The separated solid precipitate was filtered off, dried and recrystallized from DMF/EtOH to give compound **9** in 88% yield; a white solid; mp 250-252 °C (DMF/EtOH); IR (KBr): $\nu_{\max}/\text{cm}^{-1} = 3421$ (NH), 2197 (CN), 1691 (C=O); ^1H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 4.10 (s, 2H, CH₂), 8.71 (d, $J = 2.2$ Hz, 1H, C₅-H triazine), 8.90 (d, $J = 2.2$ Hz, 1H, C₆-H triazine), 10.64 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 26.2, 117.3, 141.5, 150.6, 158.4, 168.8; MS m/z (%): 163 (M⁺, 15.4); Anal. Calcd for C₆H₅N₅O (163.14): C, 44.17; H, 3.09; N, 42.93%. Found: C, 44.23; H, 3.13; N, 42.92%.

Synthesis of 8-amino-6*H*-pyrimido[1,2-*b*][1,2,4]triazin-6-one (10)

Compound **9** (1.63 g, 0.01 mol), in glacial acetic acid (15 mL) was heated under reflux for 12 h. The reaction mixture was cooled and the separated solid was collected by filtration and recrystallized from DMF/EtOH to give compound **10** in 82% yield; yellowish brown powder; mp > 300 °C (DMF/EtOH); IR (KBr): $\nu_{\max}/\text{cm}^{-1} = 3375, 3319$ (NH₂), 1676 (C=O), 1633 (C=N); ^1H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 6.42 (s, 1H, C₇-H), 6.66 (s, 2H, NH₂), 8.32 (d, $J = 2.2$ Hz, 1H, C₃-H), 8.66 (d, $J = 2.2$ Hz, 1H, C₂-H); ^{13}C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 78.6, 141.4, 150.5, 158.6, 171.2, 182.1; MS m/z (%): 163 (M⁺, 12.0); Anal. Calcd for C₆H₅N₅O (163.14): C, 44.17; H, 3.09; N, 42.93%. Found: C, 44.27; H, 3.17; N, 42.99%.

Synthesis of 8*H*-pyrimido[1,2-*b*][1,2,4]triazin-6-amine (11)

To a solution of compound **1** (0.96 g, 0.01 mol) in DMF/AcOH (11 mL, 10:1), 3-bromopropanenitrile (0.82 mL, 0.01 mol) was added. The reaction mixture was heated under reflux for 8 h. The reaction mixture was poured onto crushed ice. The obtained solid product was collected by filtration, dried and crystallized from EtOH to give compound **11** in 55% yield; reddish brown crystals; mp > 300 °C (EtOH); IR (KBr): $\nu_{\max}/\text{cm}^{-1} = 3322, 3195$ (NH₂), 1626 (C=N); ^1H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 4.13 (d, $J = 6.6$ Hz, 2H, C₆-H), 5.69 (t, $J = 6.8$ Hz, 1H, C₇-H), 6.65 (s, 2H, NH₂), 8.41 (d, $J = 2.2$ Hz, 1H, C₃-H), 8.66 (d, $J = 2.2$ Hz, 1H, C₂-H); ^{13}C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 51.8, 88.4, 140.4, 150.5, 158.2, 160.3; MS m/z (%): 149 (M⁺, 55.0); Anal. Calcd for C₆H₇N₅ (149.16): C, 48.32; H, 4.73; N, 46.95%.

Found: C, 48.40; H, 4.78; N, 47.01%.

Synthesis of 6-(2,5-dimethoxyphenyl)-8-imino-8*H*-pyrimido[1,2-*b*][1,2,4]triazine-7-carbonitrile (**15**)

2-(2,5-Dimethoxybenzylidene)malononitrile (**12**) (2.14 g, 0.01 mol) was added to a mixture of compound **1** (0.96 g, 0.01 mol) in sodium ethoxide (prepared from 0.23 g of sodium metal and 20 mL of absolute EtOH). The reaction mixture was heated under reflux for 8 h, left to cool to room temperature and poured onto ice-cold water containing drops of 1N HCl. The precipitate that formed was collected by filtration, washed with EtOH and recrystallized from EtOH to afford compound **15** in 68% yield; yellow crystals; mp 100-102 °C (EtOH); IR (KBr): $\nu_{\max}/\text{cm}^{-1}$ = 3249 (NH), 2219 (CN), 1629 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 3.71 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 6.85-7.00 (m, 3H, Ar-H), 8.32 (d, *J* = 2.2 Hz, 1H, C₃-H), 8.69 (d, *J* = 2.2 Hz, 1H, C₂-H), 9.87 (s, 1H, NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 55.2, 56.4, 90.6, 115.2, 116.4, 117.5, 118.7, 120.1, 140.5, 150.1, 151.4, 152.6, 158.2, 160.8, 163.4; MS *m/z* (%): 308 (M⁺, 21.0); Anal. Calcd for C₁₅H₁₂N₆O₂ (308.30): C, 58.44; H, 3.92; N, 27.26%. Found: C, 58.53; H, 3.99; N, 27.31%.

Synthesis of 6-methyl-8*H*-pyrimido[1,2-*b*][1,2,4]triazin-8-one (**17**)

To a mixture of compound **1** (0.96 g, 0.01 mol) in glacial acetic acid (25 mL), an appropriate amount of 1,3-dicarbonyl compounds (ethyl acetoacetate or acetoacetanilide) (0.01 mol) was added. The reaction mixture was refluxed for 10-12 h (the reaction progress was monitored by TLC), and then poured into crushed ice. The solid product was collected by filtration, dried and recrystallized from DMF/EtOH to give the same product **17** in 77% yield in case of using ethyl acetoacetate and 61% yield in case of using acetoacetanilide; brown powder; mp 268-270 °C (DMF/EtOH); IR (KBr): $\nu_{\max}/\text{cm}^{-1}$ = 1675 (C=O), 1640 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 2.32 (s, 3H, CH₃), 6.56 (s, 1H, C₇-H), 8.34 (d, *J* = 2.2 Hz, 1H, C₃-H), 8.67 (d, *J* = 2.2 Hz, 1H, C₂-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 28.2, 106.2, 141.5, 150.8, 156.5, 158.6, 164.8; MS *m/z* (%): 162 (M⁺, 38.0); Anal. Calcd for C₇H₆N₄O (162.15): C, 51.85; H, 3.73; N, 34.55%. Found: C, 51.95; H, 3.79; N, 34.62%.

Synthesis of 9,9-dimethyl-8,9-dihydro-7*H*-[1,2,4]triazino[2,3-*a*]quinazolin-7-one (**19**)

To a solution of compound **1** (0.96 g, 0.01 mol) in glacial acetic acid (15 mL), 2-((dimethylamino)-methylene)-5,5-dimethylcyclohexane-1,3-dione (**18**) (1.95 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 8 h and then cooled to room temperature. When the reaction mixture was triturated with EtOH (10 mL), the solid product was precipitated and collected by filtration, dried and crystallized from EtOH to give compound **19** in 65% yield; brown powder; mp 296-298 °C (EtOH); IR (KBr): $\nu_{\max}/\text{cm}^{-1}$ = 1693 (C=O), 1648 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 1.18 (s, 3H, CH₃), 1.22 (s, 3H, CH₃), 2.43 (s, 2H, CH₂), 5.65 (s, 1H, C₁₀-H), 8.31 (d, *J* = 2.2 Hz, 1H, C₃-H), 8.65 (d, *J* = 2.2 Hz, 1H, C₂-H), 8.93 (s, 1H, C₆-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 27.8, 28.4, 35.6, 50.8, 116.3, 140.3, 141.2, 143.1, 144.6, 150.5, 158.3, 192.6; MS *m/z* (%): 228 (M⁺, 25.2); Anal. Calcd for

C₁₂H₁₂N₄O (228.26): C, 63.15; H, 5.30; N, 24.55%. Found: C, 63.18; H, 5.38; N, 24.60%.

Synthesis 10-(pyridin-3-yl)-6-(pyridin-3-ylmethylene)-6,8,9,10-tetrahydro-7H-[1,2,4]triazino[3,2-b]-quinazoline (21)

A mixture of compound **1** (0.96 g, 0.01 mol) and 2,6-bis(pyridin-3-ylmethylene)cyclohexan-1-one (**20**) (2.76 g, 0.01 mol) in ethanolic potassium hydroxide (0.5 g KOH dissolved in 25 mL EtOH) was refluxed for 6 h, and then allowed to cool to room temperature. The solid product so formed was filtered off, washed with water, dried well, and recrystallized from EtOH to afford compound **21** in 52% yield; yellow crystals; mp 138-140 °C (EtOH); IR (KBr): $\nu_{\max}/\text{cm}^{-1}$ = 1634 (C=N), 1592 (C=C); ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 1.84 (m, 2H, CH₂), 2.24 (t, 2H, CH₂), 2.73 (t, 2H, CH₂), 3.94 (s, 1H, C₆-H), 6.64 (s, 1H, vinylic CH), 7.56-8.64 (m, 8H, Ar-H), 8.34 (d, 1H, *J* = 2.2 Hz, C₃-H), 8.67 (d, 1H, *J* = 2.2 Hz, C₂-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 26.4, 28.6, 31.2, 64.2, 114.3, 122.6, 124.8, 126.0, 132.6, 133.8, 134.7, 140.3, 143.7, 145.4, 146.5, 147.6, 148.8, 150.6, 151.2, 158.3; MS *m/z* (%): 354 (M⁺, 23.0); Anal. Calcd for C₂₁H₁₈N₆ (354.42): C, 71.17; H, 5.12; N, 23.71%. Found: C, 71.24; H, 5.21; N, 23.75%.

Synthesis of 6-(naphtho[2,1-*b*]furan-2-yl)imidazo[1,2-*b*][1,2,4]triazine (23)

To a solution of compound **1** (0.96 g, 0.01 mol) in DMF/AcOH (15 mL, 12:3), 2-bromo-1-(naphtho[2,1-*b*]furan-2-yl)ethan-1-one (**22**) (2.87 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 8 h. The mixture was poured onto crushed ice. The obtained solid product was collected by filtration, dried and recrystallized from EtOH to give compound **23** in 37% yield; reddish brown powder; mp > 300 °C (EtOH); IR (KBr): $\nu_{\max}/\text{cm}^{-1}$ = 1623 (C=N), 1599 (C=C); ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.08 (s, 1H, furan-H), 7.59-8.33 (m, 7H, Ar-H), 8.54 (d, *J* = 2.2 Hz, 1H, C₃-H), 8.65 (d, *J* = 2.2 Hz, 1H, C₂-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 100.3, 113.4, 120.2, 122.3, 124.7, 125.8, 126.2, 127.4, 128.5, 130.3, 138.6, 140.4, 149.3, 150.6, 156.4, 158.5; MS *m/z* (%): 286 (M⁺, 26.0); Anal. Calcd for C₁₇H₁₀N₄O (286.29): C, 71.32; H, 3.52; N, 19.57%. Found: C, 71.34; H, 3.55; N, 19.63%.

REFERENCES

1. E. Abd El-Aal, H. A. Fattah, N. Osman, and I. Seliem, *J. Chem. Res.*, 2016, **40**, 47.
2. P. Gahtori, S. K. Ghosh, B. Singh, U. P. Singh, H. R. Bhat, and A. Uppal, *Saudi Pharm. J.*, 2012, **20**, 35.
3. J. C. A. Hunt, E. Briggs, E. D. Clarke, and W. G. Whittingham, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5222.
4. J. N. Sangshetti and D. B. Shinde, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 742.
5. K. Ban, S. Duffy, Y. Khakham, V. M. Avery, A. Hughes, O. Montagnat, K. Katneni, E. Ryan, and J. B. Baell, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6024.
6. H. Irannejad, A. Kebriaieezadeh, A. Zarghi, F. Montazer-Sadegh, A. Shafiee, A. Assadieskandar,

- and M. Amini, *Bioorg. Med. Chem.*, 2014, **22**, 865.
7. P. Ahuja and N. Siddiqui, *Eur. J. Med. Chem.*, 2014, **80**, 509.
 8. H. Irannejad, M. Amini, F. Khodagholi, N. Ansari, S. K. Tusi, M. Sharifzadeh, and A. Shafiee, *Bioorg. Med. Chem.*, 2010, **18**, 4224.
 9. F. Krauth, H.-M. Dahse, H.-H. Rüttinger, and P. Froberg, *Bioorg. Med. Chem.*, 2010, **18**, 1816.
 10. V. Lozano, L. Aguado, B. Hoorelbeke, M. Renders, M.-J. Camarasa, D. Schols, J. Balzarini, A. San-Félix, and M.-J. Pérez-Pérez, *J. Med. Chem.*, 2011, **54**, 5335.
 11. P. Zhan, X. Li, Z. Li, X. Chen, Y. Tian, W. Chen, X. Liu, C. Pannecouque, and E. De Clercq, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 7155.
 12. T. Akbarzadeh, S. Noushini, S. Taban, M. Mahdavi, M. Khoshneviszadeh, M. Saeedi, S. Emami, M. Eghtedari, Y. Sarrafi, M. Khoshneviszadeh, M. Safavi, K. Divsalar, M. H. Moshafi, A. Asadipour, R. Sabourian, N. Edraki, O. Firouzi, R. Miri, A. Shafiee, and A. Foroumadi, *Mol. Divers.*, 2015, **19**, 273.
 13. D.-J. Fu, J. Song, Y.-H. Hou, R.-H. Zhao, J.-H. Li, R.-W. Mao, J.-J. Yang, P. Li, X.-L. Zi, Z.-H. Li, Q.-Q. Zhang, F.-Y. Wang, S.-Y. Zhang, Y.-B. Zhang, and H.-M. Liu, *Eur. J. Med. Chem.*, 2017, **138**, 1076.
 14. K. Sztanke, J. Rzymowska, M. Niemczyk, I. Dybała, and A. E. Koziół, *Eur. J. Med. Chem.*, 2006, **41**, 539.
 15. K. Pattabiraman, R. El-Khoury, K. Modi, L. R. McGee, and D. Chow, *Tetrahedron Lett.*, 2009, **50**, 1571.
 16. H. M. Refat and A. A. Fadda, *Heterocycles*, 2015, **91**, 1212.
 17. L. Hwang, R. Wu, C. Jane, and G. Lee, *Anal. Sci.*, 2003, **19**, x73.
 18. R. M. Abdel-Rahman, J. M. Morsy, F. Hanafy, and H. A. Amene, *Pharmazie*, 1999, **54**, 347.
 19. W. A. Spitzer, F. Victor, G. D. Pollock, and J. S. Hayes, *J. Med. Chem.*, 1988, **31**, 1590.
 20. S. Nagai, T. Ueda, M. Takemura, A. Nagatsu, N. Murakami, and J. Sakakibara, *J. Heterocycl. Chem.*, 1998, **35**, 293.
 21. S. A. Yermolayev, N. Y. Gorobets, O. V. Shishkin, S. V. Shishkina, and N. E. Leadbeater, *Tetrahedron*, 2011, **67**, 2934.
 22. M. Loubidi, J. Jouha, Z. Tber, M. Khouili, F. Suzenet, M. Akssira, M. A. Erdogan, F. A. Köse, T. Dagcı, G. Armagan, L. Saso, and G. Guillaumet, *Eur. J. Med. Chem.*, 2018, **145**, 113.
 23. A. Rykowski, H. C. Van der Plas, and C. H. Stam, *Acta Crystallogr.*, 1977, **B33**, 274.
 24. A Martel and F Tremblay, U.S. Patent, 2017, 9, 598, 419.
 25. P. Barraclough, D. Firmin, J. C. Lindon, M. S. Nobbs, P. N. Sanderson, S. Smith, and J. M. Gillam, *Magn. Reson. Chem.*, 1991, **29**, 468.

26. S. R. Jain and A. Kar, *Planta Med.*, 1971, **20**, 118.
27. M. Haroun, C. Tratratt, K. Kositzki, E. Tsolaki, A. Petrou, B. Aldhubiab, M. Attimarad, S. Harsha, A. Geronikaki, K. N. Venugopala, H. S. Elsewedy, M. Sokovic, J. Glamoclija, and A. Ciric, *Curr. Top. Med. Chem.*, 2018, **18**, 75.
28. I. S. Nosulenko, O. Y. Voskoboynik, G. G. Berest, S. I. Kovalenko, O. M. Kamyshnyi, and N. M. Polishchuk, *Visnik farmacii.*, 2015, **1**, 11 (ISSN 1562-7241).
29. L. Zhang, Q. Chen, X.-Q. Li, S.-Q. Wu, J.-L. Wan, and G.-P. Ouyang, *J. Heterocycl. Chem.*, 2018, **55**, 743.
30. S. J. Sabounchei, P. Shahriary, S. Salehzadeh, Y. Gholiee, and A. Chehregani, *Compt. Rend. Chim.*, 2015, **18**, 564.