Synthesis of Some Novel Pyrazolo[1,5-*a*]pyrimidine, 1,2,4-Triazolo[1,5-*a*]pyrimidine, Pyrido[2,3-*d*]pyrimidine, Pyrazolo[5,1-*c*]-1,2,4-triazine and 1,2,4-Triazolo[5,1-*c*]-1,2,4-triazine Derivatives Incorporating a Thiazolo[3,2-*a*]benzimidazole Moiety

Hatem A. Abdel-Aziz* [a], Nehal A. Hamdy [a], Ahmad M. Farag [b] and Issa M. I. Fakhr [a]

[a] Applied Organic Chemistry Department, National Research Centre, Dokki, Cairo 12622, Egypt
[b] Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt

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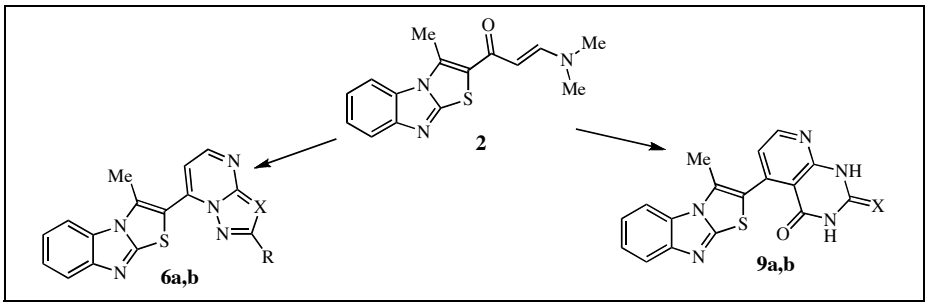

E-3-(*N*,*N*-Dimethylamino)-1-(3-methylthiazolo[3,2-*a*]benzimidazol-2-yl)prop-2-en-1-one (**2**) was synthesized by the reaction of 1-(3-methylthiazolo[3,2-*a*]benzimidazol-2-yl)ethanone (**1**) with dimethylformamide-dimethylacetal. The reaction of **2** with 5-amino-3-phenyl-1*H*-pyrazole (**4a**) or 3-amino-1,2,4-(1*H*)-triazole (**4b**) furnished pyrazolo[1,5-*a*]pyrimidine and 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives **6a** and **6b**, while the reaction of enaminone **2** with 6-aminopyrimidine derivatives **7a,b** afforded pyrido[2,3-*d*]pyrimidine derivatives **9a,b**, respectively. The diazonium salts **11a** or **11b** coupled with compound **2** to yield the pyrazolo[5,1-*c*]-l,2,4-triazine and l,2,4-triazolo[5,1-*c*]-l,2,4-triazine derivatives **13a** and **13b**. Some of the newly synthesized compounds exhibited a moderate effect against some bacterial and fungal species.

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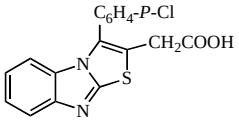
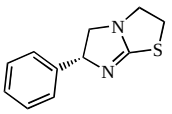
INTRODUCTION

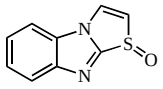
Tilomisole (WY-18,251) is one of the most important derivatives [1,2] among thiazolo[3,2-*a*]benzimidazole derivatives which shows antinflammatory [3], and immunomodulatory [4] activities, since the thiazolo-[3,2-*a*]benzimidazole system is similar in part to levamisole a well-known immunomodulator [5]. Recently, the gastric antisecretory activity of thiazolo-[3,2-*a*]benzimidazol-1-oxide (WY-26,769) was reported [6]. On the other hand, thiazolo[3,2-*a*]benzimidazole derivatives were found to have strong biological activities including antibacterial [7-9], anti-inflammatory [10], antiulcer [11,12] and antiviral [13,14] activities. Furthermore, some thiazolo[3,2-*a*]benzimidazole derivatives used for treatment of cancer [15], cerebral infarction [16], neurogenic pain [17], bone diseases [18] and mGluR1 related diseases (epilepsy, inhibition of nerve cell death, Parkinson's disease, migraine headache and anxiety disorder) [19].



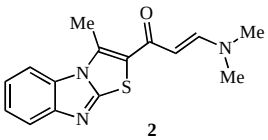
Tilomisole (WY-18,251)



Levamisole



(WY-26,769)



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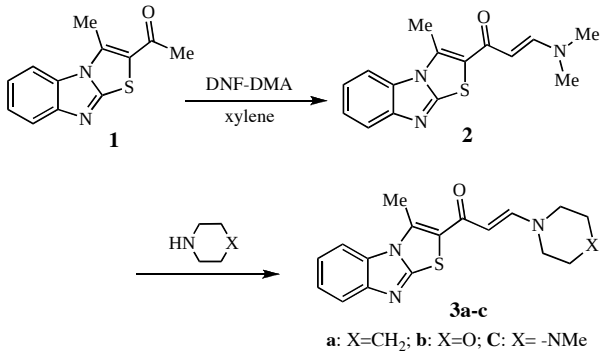
In an attempt to achieve new compounds with possible antimicrobial properties [20,21] and in our continuous study on the synthesis of new biologically active heterocycles [20-25], we reported herein the synthesis of some novel heterocycles incorporating a thiazolo[3,2-*a*]-benzimidazole moiety starting from *E*-3-(*N*,*N*-dimethylamino)-1-(3-methylthiazolo[3,2-*a*]benzimidazol-2-yl)prop-2-en-1-one (**2**) to evaluate their antimicrobial properties.

RESULTS AND DISCUSSION

1-(3-Methylthiazolo[3,2-*a*]benzimidazol-2-yl)ethanone (**1**) was treated with dimethylformamide-dimethylacetal (DMF-DMA), in dry xylene, at reflux temperature, it afforded a yellow crystalline product that was identified

as *E*-3-(*N*,*N*-dimethylamino)-1-(3-methylthiazolo[3,2-*a*]-benzimidazol-2-yl)prop-2-en-1-one (**2**) (Scheme I). The structure of the latter product was established on the basis of its elemental analysis and spectral data (ir, ^{1}H nmr, ^{13}C nmr and ms). For example, compound **2** assigned the *E* conformation on the basis of its ^{1}H nmr spectrum which showed the olefinic protons as two duplets at δ 5.37, 5.41 (=CH-CO) and δ 7.73, 7.77 (=CH-N) with J=12.0 Hz, as reported for such *E*-coupled protons, these finding are in complete agreement with that of recent reports [26,27]. Also, ^{1}H nmr revealed three singlet signals corresponding to three methyl groups at δ 2.92, 3.07 and 3.17 in addition to the aromatic protons. Its mass spectrum revealed a peak corresponding to its molecular ion at *m*/*z* 285 (M^+).

Scheme I

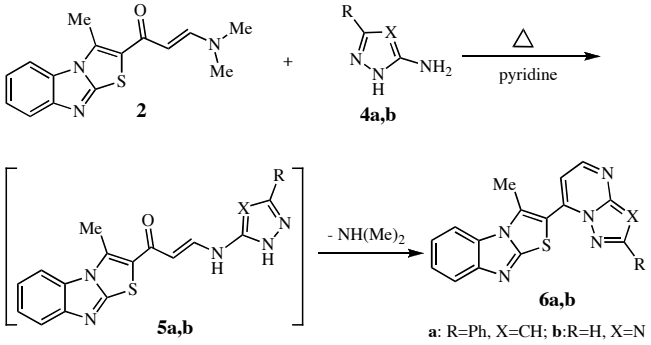


Next, the enaminone **2** reacted with some secondary amines namely piperidine, morpholine or 1-methyl-piperazine in refluxing ethanol to afford the corresponding tertiary amines **3a-c**, respectively (Scheme I). The ir spectra of the latter products showed carbonyl absorption bands in the region 1643-1639 cm^{-1}. Their mass spectra showed, in each case, a peak corresponding to their molecular ions. Their ^{1}H nmr spectra are free of signals characteristic for the dimethylamine protons in addition to the appearance of two doublet signals (J=12.3 Hz) corresponding to the *E*-coupled olefinic protos [27] (cf. Experimental part).

The behavior of enaminone **2** towards some heterocyclic amines as convenient access for synthesis a variety of fused heterocyclic systems [28,29] was investigated. Thus, when compound **2** was treated with 5-amino-3-phenyl-1*H*-pyrazole (**4a**) or 3-amino-1,2,4-(1*H*)-triazole (**4b**) in refluxing pyridine, it furnished the pyrazolo[1,5-*a*]pyrimidine and 1,2,4-triazolo[1,5-*a*]-pyrimidine derivatives, **6a** and **6b**, (Scheme II).

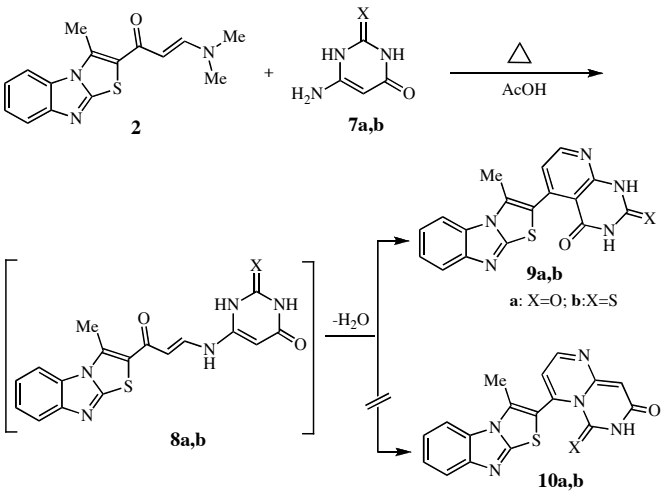
The structures of the latter products were confirmed on the basis of their elemental analyses and spectral data (ir, ^{1}H nmr, ^{13}C nmr and ms). For example, the ir spectrum of **6a** revealed the lack of a band corresponding to carbonyl function, while its ^{1}H nmr spectrum showed singlet signal duo to pyrazole proton at δ 5.23. Its mass spectrum revealed a peak corresponding to its molecular ion at *m*/*z* 381 (M^+).

Scheme II



Furthermore, the reaction of enaminone **2** with 6-amino-1*H*-pyrimidin-2,4-dione (**7a**) or 6-amino-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (**7b**) in refluxing acetic acid resulted in the formation of pyrido[2,3-*d*]pyrimidines **9a** and **9b** (Scheme III). Their ^{1}H nmr spectra revealed two signals (D_2O exchangeable) assigned to 2NH protons, whereas their mass spectra showed, in each case, a peak corresponding to their molecular ion values. The latter reaction was assumed to proceed through an initial *Michael* type addition of the amino group in pyrimidines **7a,b** to the double bond in enaminone **2** followed by the elimination of dimethylamine to afford the non-isolable intermediates **8a,b**. which may be cyclized into the pyrido[2,3-*d*]pyrimidine derivatives **9a,b** or pyrimido[1,6-*a*]pyrimidine derivatives **10a,b** (Scheme III). However,

Scheme III

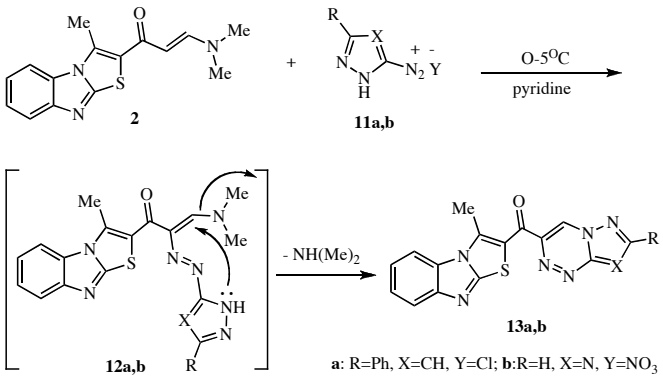


structures **10a,b** were easily excluded on the basis of the spectral data of the isolated products.

Finally, The enaminone **2** reacted with the diazonium salt of 3-phenyl-5-amino-1*H*-pyrazole **11a** or 5-amino-

l,2,4-(1*H*)-triazole [30,31] to afford the non-isolable azo-coupling intermediates **12a,b** which cyclized *via* dimethylamine elimination to yield the pyrazolo[5,1-*c*]-l,2,4-triazine and 1,2,4-triazolo[5,1-*c*]-l,2,4-triazine derivatives **13a** and **13b** in good yields (Scheme IV).

Scheme IV



The ir spectra of latter compounds revealed, in each case, the lack of bands corresponding to endo-cyclic NH and showed carbonyl absorption bands in the region 1648-1639 cm^{-1}. Their mass spectra showed, in each case, a peak corresponding to the molecular ions (*cf.* Experimental part).

Antimicrobial Evaluation. The antibacterial and antifungal activities were carried out at the Regional Centre for Mycology and Biotechnology at Al-Azhar University, Cairo, Egypt. Some of the newly synthesized compounds were screened for their antimicrobial activity using the diffusion agar technique [32], where six compounds were tested against four fungal species namely *Aspergillus fumigatus (Af), Penicillium italicum (Pi), Syncephalastrum racemosum (Sr)* and *Candida albicans (Ca)* as well as against four bacterial species namely *Staphylococcus aureus (Sa), Pseudomonas aeruginosa (Pa), Bacillus subtilis (Bs)* and *Escherichia coli (Ec)* for their antimicrobial activity using 5 mg/mL of each compound in dimethylformamide. Inhibition zone diameter (IZD) in cm was taken as the criterion for antimicrobial activity. The antimicrobial activity was assayed biologically using a spore suspension of the fungal species (1 mL of sterile water containing approximately 10^8 conidia) or spreading bacterial suspension over a solidified malt agar medium. The layer was allowed to set for 30 min. A solution of each of the tested compounds (5 mg/mL) was placed onto sterile 5 mm filter paper discs and allowed to dry, then the discs were placed onto the center of the malt agar plate and incubated at the optimum incubation temperature, 28±2°C. A clear zone around the disc was taken as an indication of the inhibition of the test organism growth. The size of the clear zone is proportional to the inhibitory action of the compound under investigation. The fungicide *Terbinafin* and the bactericide *Chloramphenicol* were used as references to evaluate the potency of the tested compounds under the same conditions. Measurements were considered after 72 h for fungi and 24 h for bacteria. The results are contained in Table 1.

Table 1

Antimicrobial activities of the tested compounds.

No. [a]	Inhibitions [b]							
	Af	*Pi*	*Sr*	*Ca*	*Sa*	*Pa*	*Bs*	*Ec*
3b	+	-	+	-	-	-	+	++
6a	+	+	++	-	+	-	-	+
6b	-	-	+	+	+	-	-	+
9b	+	+	++	-	++	+	-	++
13a	+	-	+	-	-	+	-	-
St. [c]	+++	+++	+++	++	++	+++	+++	++

[a] Compound **13b** revealed no activities against all species. [b] IZD beyond control / (sign): 0.1-0.5 cm / (+), 0.6-1.0 cm / (++), 1.1-1.5 cm / (+++) and 0 cm / (-). [c] The fungicide *Terbinafin* and the bactericide *Chloramphenicol* were used as standards.

The results of antimicrobial activity showed that compound **9b** exhibited a moderate effect against *Syncephalastrum racemosum (Sr), Staphylococcus aureus (Sa)* and *Escherichia coli (Ec)*. Also, both compound **3b** and **6a** showed a moderate effect against *Escherichia coli (Ec)* and *Syncephalastrum racemosum (Sr), respectively.* However, the activity of the tested compounds is less than those of the standard agents used (Table 1).

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^1H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated dimethylsulphoxide ($DMSO-d_6$). Chemical shifts are quoted in δ and were related to that of the solvents. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 1-(3-Methyl-thiazolo[3,2-*a*]benzimidazol-2-yl)ethanone (**1**) [33] and 5-amino-3-phenyl-1*H*-pyrazole (**4a**) [34] were prepared by the reported methods. 3-Amino-1,2,4-(1*H*)-triazole (**4b**), 6-amino-1*H*-pyrimidin-2,4-dione (**7a**) or 6-amino-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (**7b**) were used as obtained commercially.

***E*-3-(*N*,*N*-Dimethylamino)-1-(3-methylthiazolo[3,2-*a*]benz-imidazol-2-yl)prop-2-en-1-one (2).** A mixture of 1-(3-methylthiazolo[3,2-*a*]benzimidazol-2-yl)ethanone (**1**) (2.3 g, 10 mmol) and dimethylformamide-dimethylacetal (DMF-DMA) (1.34 g, 10 mmol) in dry xylene (50 mL) was refluxed for 5 h. The solvent was evaporated and the resulting yellow crystals were taken by ether, collected by filtration, washed thoroughly with ether, dried and finally recrystallized from ethanol/ dimethylformamide to afford the enaminone **2** in 62% yield; mp:

240-241°C; ir: 1624 (C=O), 1535 (C=N) cm^{-1}; ^{13}C nmr (DMSO-d_6): δ 14.9 (-CH_3), 44.6, 44.7 (-N=(CH_3)$_2$), 108.6 (-S-*C*=C-CH_3), 110.1 (-CO-*C*H=), 121.8, 122.5, 124.9, 125.2, 130.2, 137.6 (C_6H_4), 148.4 (C of imidazole), 149.1 (=*C*H-N), 154.7 (-S-C=*C*-CH_3), 180.4 (C=O); ^1H nmr (DMSO-d_6): δ 2.92 (s, 3H, CH_3), 3.07 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 5.37, 5.41 (d, 1H, J=12.0 Hz, -CO-CH=), 7.27-7.70 (m, 3H ArH), 7.73, 7.77 (d, 1H, J=12.0 Hz, =CH-N-), 8.00-8.02 (m, 1H ArH); ms: m/z 286 (M^++1,), 285 (M), 241, 188, 136, 98, 71, 55. *Anal.* Calcd. for $C_{15}H_{15}N_3OS$: C, 63.13; H, 5.30; N, 14.72; S, 11.24. Found: C 63.44; H, 5.02; N, 14.95; S, 11.13.

General Procedure for the Reaction Enaminone 2 with Secondary Amines. A mixture of *E*-3-(*N,N*-dimethylamino)-1-(3-methylthiazolo[3,2-*a*]benzimidazol-2-yl)prop-2-en-1-one (**2**) (1.93 g, 5 mmol) and the appropriate secondary amine (piperidine, morpholine or 1-methylpiperazine) (3 mL) in ethanol (30 mL) was refluxed for 4 h, then left to cool. The precipitated product was collected by filtration, washed with ethanol and dried. Recrystallization from ethanol/ dimethylformamide afforded **3a, 3b** and **3c** in 88, 74 and 83% yield, respectively.

***E*-1-(3-Methylthiazolo[3,2-*a*]benzimidazol-2-yl)-3-(piperidin-1-yl)prop-2-en-1-one (7a).** This compound was obtained as yellow needles, mp 233-235°C; ir: 1639 (C=O), 1576 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.34-2.49 (m, 6H, piperidine), 3.01 (s, 3H, CH_3), (m, 4H, piperidine), 5.56, 5.60 (d, 1H, J=12.3 Hz, -CO-CH=), 7.25-7.70 (m, 3H ArH), 7.71, 7.75 (d, 1H, J=12.3 Hz, =CH-N-), 8.02-8.04 (m, 1H ArH); ms: m/z 326 (M^++1), 325 (M^+), 188, 83. *Anal.* Calcd. for $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.88; N, 12.91; S, 9.85. Found: C, 66.12; H, 5.65; N, 12.60; S, 9.97.

***E*-1-(3-Methylthiazolo[3,2-*a*]benzimidazol-2-yl)-3-(morpholin-4-yl)prop-2-en-1-one (7b).** This compound was obtained as pale yellow needles, mp 267-269°C; ir: 1643 (C=O), 1551 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.55-2.59 (m, 4H, morpholine), 3.03 (s, 3H, CH_3), (m, 4H, morpholine), 5.56, 5.60 (d, 1H, *J*=12.2 Hz, -CO-CH=), 7.23-7.70 (m, 3H ArH), 7.71, 7.75 (d, 1H, *J*=12.3 Hz, =CH-N-), 8.01-8.03 (m, 1H ArH); ms: m/z 328 (M^++1), 327 (M^+), 140, 118, 85. *Anal.* Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.37; H, 5.23; N, 12.83; S, 9.79. Found: C, 62.54; H; 5.37; N, 12.64; S, 9.56.

***E*-1-(3-Methylthiazolo[3,2-*a*]benzimidazol-2-yl)-3-(4-methylpiperazin-1-yl)prop-2-en-1-one (7c).** This compound was obtained as pale yellow needles, mp 195-197°C; ir: 1642 (C=O), 1566 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.22 (s, 3H, CH_3 piperazine), 2.37-2.40 (m, 4H, piperazine) 3.08 (s, 3H, CH_3), 3.45-3.50 (m, 4H, piperazine), 5.57, 5.61 (d, 1H, J=12.3 Hz, -CO-CH=), 7.23-7.70 (m, 3H ArH), 7.70, 7.74 (d, 1H, J=12.3 Hz, =CH-N-), 8.02-8.04 (m, 1H ArH); ms: m/z 341 (M^++1), 340 (M^+), 241, 201, 71, 70. *Anal.* Calcd. for $C_{18}H_{20}N_4OS$: C, 63.50; H, 5.92; N, 16.46; S, 9.42. Found: C, 63.73; H, 6.01; N, 16.11; S, 9.60.

General Procedure for the Reaction of Enaminone 2 with Heterocyclic Amines 4a,b. A mixture of enaminone **2** (2.85 g, 10 mmol) and the appropriate heterocyclic amine 5-amino-3-1*H*-phenylpyrazole (**4a**) or 3-amino-l,2,4-(1*H*)-triazole (**4b**) (10 mmol) in pyridine (25 mL) was refluxed for 12 h, then left to cool. The reaction mixture was poured into cold water and the solid product was collected by filtration, washed with water, dried and finally recrystallized from dimethylformamide/H_2O to afford the corresponding pyrazolo[1,5-*a*]pyrimidine and triazolo[1,5-*a*]pyrimidine, derivatives **6a** and **6b** in 72 and 66% yield, respectively.

3-Methyl-2-(2-phenyl-pyrazolo[1,5-*a*]pyrimidin-7-yl)thiazolo[3,2-*a*]benzimidazole (6a). This compound was obtained as yellow crystals, mp >300°C; ir: 1612 (C=N) cm^{-1}; ^{13}C nmr (DMSO-d_6): δ 15.1 (-CH_3), 94.2 (C of pyrazole), 109.7, 113.9, 114.0, 116.0, 123.6, 123.7, 125.4, 126.3, 126.4, 129.0, 129.4, 130.1, 131.9, 136.0, 139.2, 146.0, 149.7, 150.0, 154.2, 154.6; ^1H nmr (DMSO-d_6): δ 3.11 (s, 3H, CH_3), 5.23 (s, 1H, pyrazole), 7.04-8.27 (m, 10H; 9 ArH and 1H, J=4.2 Hz, pyrimidine), 8.66, 8.67 (d, 1H, J=4.2 Hz, pyrimidine); ms: m/z 382 (M^++1), 381 (M^+), 274, 240, 89, 77. *Anal.* Calcd. for $C_{22}H_{15}N_5S$: C, 69.27; H, 3.96; N, 18.36; S, 8.41. Found: C, 69.50; H, 4.12; N, 18.59; S, 8.26.

3-Methyl-2-(1,2,4-triazolo[1,5-*a*]pyrimidin-7-yl)thiazolo-[3,2-*a*]benzimidazole (6b). This compound was obtained as yellow crystals, mp 290-292°C; ir: 1616 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.02 (s, 3H, CH_3), 7.34-8.14 (m, 5H, 4 ArH and 1H, J=3.9 Hz, pyrimidine), 8.78 (s, 1H, triazole), 8.97, 8.98 (d, 1H, J=3.9 Hz, pyrimidine); ms: m/z 306 (M^+), 242, 186, 118, 51. *Anal.* Calcd. for $C_{15}H_{10}N_6S$: C, 58.81; H, 3.29; N, 27.43; S, 10.47. Found: C, 58.64; H, 3.51; N, 27.42; S, 10.23.

General procedure for the Reaction of Enaminone 2 with Aminopyrimidine derivatives 7a,b. A mixture of the enaminone **2** (2.85 g, 10 mmol) and the appropriate aminopyrimidine derivatives **7a** or **7b** (10 mmol) in acetic acid (25 mL) was refluxed for 12 h, then left to cool. The solid product filtered off, washed with ethanol, dried and finally recrystallized from dimethylformamide/H_2O to afford the corresponding pyrido[2,3-*d*]pyrimidine derivatives **9a** and **9b** in 74 and 86% yield, respectively.

5-(3-Methylthiazolo[3,2-*a*]benzimidazol-2-yl)-1*H*-pyrido-[2,3-*d*]pyrimidine-2,4-dione (9a). This compound was obtained as orange powder, mp >300°C; ir: 3233, 3098 (2NH), 1709, 1639 (2C=O), 1616 (C=N) cm^{-1}; ^{13}C nmr (DMSO-d_6): δ 14.9 (-CH_3), 107.5, 108.5, 115.0, 121.8, 122.6, 124.9, 125.1, 130.2, 137.6, 148.1, 148.4, 149.3, 152.8, 154.2, 159.7 (C=O), 161.1 (C=O); ^1H nmr (DMSO-d_6): δ 3.16 (s, 3H, CH_3), 7.28-8.33 (m, 6H; 4 ArH and 2H pyridine), 10.56 (br. s, 1H, NH, D_2O exchangeable), 10.69 (br, s, 1H, NH, D_2O exchangeable); ms: m/z 351 (M^++2), 350 (M^++1), 349 (M^+), 240, 231, 118. *Anal.* Calcd. for $C_{17}H_{11}N_5O_2S$: C, 58.44; H, 3.17; N, 20.05; S, 9.18. Found: C, 58.53; H, 3.01; N, 19.87; S, 9.34.

5-(3-Methylthiazolo[3,2-*a*]benzimidazol-2-yl)-2-thioxo-2,3-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-4-one (9b). This compound was obtained as orange powder, mp >300°C; ir: 3216, 3105 (2NH), 1648 (C=O), 1613 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.15 (s, 3H, CH_3), 7.29-8.35 (m, 6H; 4 ArH and 2H, pyridine), 11.83 (br. s, 1H, NH, D_2O exchangeable), 12.17 (br. s, 1H, NH, D_2O exchangeable); ms: m/z 366 (M^++1), 365 (M^+), 254, 118. *Anal.* Calcd. for $C_{17}H_{11}N_5OS_2$: C, 55.88; H, 3.03; N, 19.16; S, 17.55. Found: C, 56.09; H, 3.28; N, 18.87; S, 17.70.

General Procedure for the Reaction of Enaminone 2 with Diazonium Salts of Heterocyclic Amines 11a,b. To a stirred cold solution of the enaminone **4** (0.57 g, 2 mmol) in pyridine (30 mL) was added the appropriate diazonium salt of 5-amino-3-phenyl-1*H*-pyrazole **11a** or 3-amino-l,2,4-(1*H*)-triazole **11b** (2 mmol) portion-wise over a period of 30 min at 0-5ºC. After complete addition, the reaction mixture was stirred for further 3 h at 0-5ºC. The solid that precipitated was collected by filtration, washed with water and dried. Recrystallization from dimethylformamide/H_2O afforded the corresponding fused ring system **13a** and **13b** in 82 and 74% yield, respectively.

3-Methyl-2-(7-phenyl-pyrazolo[5,1-*c*]-1,2,4-triazin-3-oyl)-thiazolo[3,2-*a*]benzimidazole (13a). This compound was obtained as yellow powder, mp >300˚C; ir: 1648 (C=O), 1602 (C=N) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.62 (s, 3H, CH_3), 6.53 (s, 1H, pyrazole), 7.27-7.81 (m, 10H; 9 ArH and 1H triazine); ms: m/z 411 (M^++1), 410 (M^+), 345, 301, 239, 134, 92, 77. *Anal.* Calcd. for $C_{22}H_{14}N_6OS$: C, 64.38; H, 3.44; N, 20.47; S, 7.81. Found: C, 64.23; H, 3.67; N, 20.31; S, 7.95.

3-Methyl-2-(1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-3-oyl)thiazolo[3,2-*a*]benzimidazole (13b). This compound was obtained as yellow crystals, mp >300˚C; ir: 1639 (C=O), 1562 (C=N) cm^{-1}; ^{13}C nmr (DMSO-d_6): δ 15.0 (-CH_3), 112.9, 122.0, 123.1, 124.4, 125.3, 130.2, 137.6, 140.4, 151.5, 154.2, 156.2, 158.2, 162.4, 189.8 (C=O); ^{1}H nmr (DMSO-d_6): δ 3.23 (s, 3H, CH_3), 6.78-8.58 (m, 6H; 4 ArH, 1H triazole and 1H triazine); ms: m/z 337 (M^++2), 336 (M^++1), 335 (M^+), 188, 144, 74. *Anal.* Calcd. for $C_{15}H_9N_7OS$: C, 53.73; H, 2.71; N, 29.24; S, 9.56. Found: C, 53.57; H, 2.52; N, 29.22; S, 9.34.

REFERENCES

[1] Rainsford, K. D. *J. Pharm. Pharmacol.* **1989**, *41*, 112.

[2] Liveridge, G. G.; Conzentino, P.; Cundy, K. C.; Sarpotdar, P. P. PCT Int Appl WO patent 93,25,190, 1993; *Chem. Abstr.* **1994**, *120*, 144167d.

[3] Eickhoff, W. M.; Engers, D. A.; Mueller, K. R. U.S. patent 96,24,336, 1996; *Chem. Abstr.* **1996**, *125*, 41845x.

[4] Gilman, S. C.; Carlson, R. P.; Daniels, J. F.; Datko, L.; Berner, P. R.; Chang. J; Lewis, A. J. *Int. J. Immunopharmacol.* **1987**, *9*, 9.

[5] Bender, P. E.; Hill, D.; Offen, P. H.; Razgaitis, K.; Lavanchy, P.; Stringer, O. D.; Sutton, B. M.; Giswold, D. E.; Dimertino, M. *J. Med. Chem.* **1985**, *28*, 1169.

[6] Dijoseph, J. F.; Palumbo, G. J.; Crossley, R.; Santili, A. A.; Nielsen, S. T. *Drug Dev. Res.* 1991, *23*, 57; *Chem. Abstr.* **1991**, *115*, 64464e.

[7] Venkatesan, A. M; Mansour, T. S.; Abe, T.; Mihira, A.; Agarwal, A.; Ushirogochi, H.; Gu, Y.; Tamai, S.; Sum, F. PCT Int Appl WO patent 03,93,280, 2002; *Chem. Abstr.* **2003**, *139*, 381302u.

[8] Oh, C.; Ham, Y.; Hong, S.; Cho, J. *Arch Pharm.* **1995**, *328*, 289.

[9] Allanson, N. M.; Leslie, B. W.; Thomson, S. Brit UK patent 2,376,944, 2001; *Chem. Abstr.* **2003**, *138*, 55966t

[10] Bender, P. E.; Hill, D.; Offen, P. H.; Razgaitis, K.; Lavanchy, P.; Stringer, O. D.; Sutton, B. M.; Giswold, D. E.; Dimertino, M. *J. Med. Chem.* **1985**, *28*, 1169.

[11] Yoshida, A.; Oda, K.; Tabata, K. Jpn Kokai Tokkyo Koho patent 03,14,566, 1991; *Chem. Abstr.* **1991**, *115*, 71660z.

[12] Crossley, R. U.S. patent 4,873,237, 1989; *Chem. Abstr.* **1990**, *112*, 198401d.

[13] Moormann, A. E.; Becker, D. P.; Flynn, D. L.; Li, H.; Villamil,C. I. U.S. patent 5,945,425, 1999; *Chem. Abstr.* **1999**, *131*, 184948t.

[14] Moormann, A. E.; Becker, D. P.; Flynn, D. L.; Li, H.; Vilamil, C. I. PCT Int Appl WO patent 95,29,897, 1995; *Chem. Abstr.* **1996**, *124*, 202255b.

[15] Mckee, T. D.; Suto, R. K. PCT Int Appl WO patent 03,73,999, 2002; *Chem. Abstr.* **2003**, *139*, 240337x.

[16] Itahana, H.; Okada, S.; Ohara, A.; Negoro, K.; Nozawa, S.; Kamikubo, T.; Sakamoto, S. Jpn Kokai Tokkyo Koho JP patent 105,085, 2002 ; *Chem. Abstr.* **2002**, *136*, 294827p.

[17] Okada, M.; Nagakura, Y.; Kiso, T.; Toya, T.; Hayashibe, S. PCT Int Appl WO patent 01,08,705, 2001; *Chem. Abstr.* **2001**, *134*, 141763y.

[18] Oku, T.; Kawai. Y.; Yatabe, T.; Sato, S.; Yamazaki, H.; Kayakiri, N.; Yoshihara, K. PCT Int Appl WO patent 97,10,219, 1997; *Chem. Abstr.* **1997**, *126*, 293352m.

[19] Itahana, H.; Fujiyasu, J.; Hayashibe, S.; Watanabe, T.; Okada, M.; Toya, T. PCT Int. Appl. WO patent 03,78,441, 2002; *Chem. Abstr.* **2003**, *139*, 261301w.

[20] Hamdy, N. A.; Abdel-Aziz, H. A.; Farag, A. M.; Fakhr, I. M. I. *Monatsch. Chem.* **2007**, *138*, 1001.

[21] Dawood, K. M.; Farag, A. M.; Abdel-Aziz, H. A. *Heteroatom Chem.* **2004**, *7*, 621.

[22] Abdel-Aziz, H. A.; Hamdy, N. A.; Farag, A. M.; Fakhr, I. M. I. *J. Chin. Chem. Soc.* **2007**, *54*, 1573.

[23] Farag, A. M.; Dawood, K. M.; Abdel-Aziz, H. A. *J. Chem. Res.* **2004**, 808.

[24] Dawood, K. M.; Farag, A. M.; Abdel-Aziz, H. A. *J. Chem. Res.* **2005**, 278.

[25] Dawood, K. M.; Farag, A. M.; Abdel-Aziz, H. A. *Heteroatom Chem.* **2007**, *18*, 294.

[26] Shaaban, M. R.; Salah, T. S.; Osman, F. H.; Farag, A. M. *J. Het. Chem.* **2007**, *44*, 177.

[27] Almazroa, S.; Elnagdi, M. H.; Salah El-Din, A. M. *J. Het. Chem.* **2004**, *41*, 267.

[28] Dawood, K. M.; Farag, A. M.; Kandeel, Z. E. *J. Chem. Res.* **1999** 88.

[29] Ghozlan, S. A. S.; Abdelhamid, I. A.; Gaber, H.; Elnagdi M. H. *J. Chem. Res.* **2004,** 789.

[30] Farag, A. M. *J. Chem. Res.* (S) **1995,** 96.

[31] Farag, A. M.; Dawood, K. M.; Kandeel, Z. E. *Tetrahedron* **1996**, *52*, 7893.

[32] El-Merabani, M. M.; El-Aaser, A. A.; Attia, M. A. *J. Planta Medica* **1972**, *36*, 150.

[33] D'Amico, J. J.; Campbell, R. H.; Guinn, E. C. *J. Org. Chem.* **1964**, *19*, 865.

[34] Takamizawa, A.; Hamashima, Y. *Yakugakyzasshi* **1964**, *84*, 1113.