HETEROCYCLES, Vol. 71, No. 8, 2007, pp. 1765 – 1777. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd March, 2007, Accepted, 23rd May, 2007, Published online, 25th May, 2007. COM-07-11060

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NOVEL PYRAZOLO[1,5-*a*]PYRIMIDINE, TRIAZOLO[1,5-*a*]PYRIMIDINE AND PYRIMIDO[1,2-*a*]BENZIMIDAZOLE DERIVATIVES

Mohamed R. Shaaban, Tamer S. Saleh, and Ahmad M. Farag*

Department of Chemistry, Faculty of Science, University of Cairo, Giza 12613, Egypt

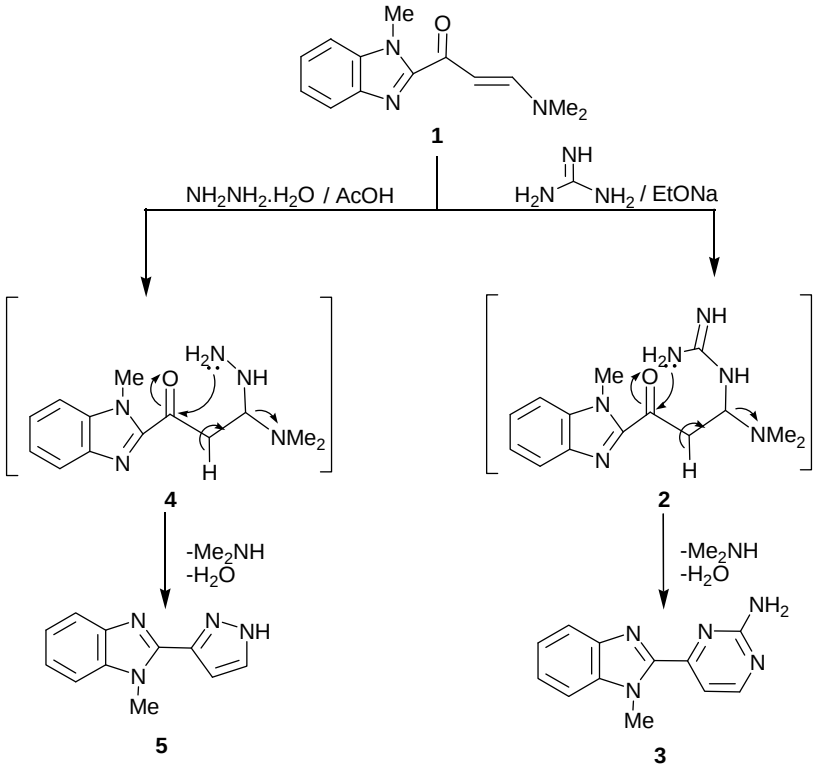
Abstract- The applicability and synthetic potency of *E*-1-(1-methylbenzimidazol-2-yl)-3-*N*,*N*-dimethylaminoprop-2-enone towards some nitrogen nucleophiles was investigated as a convenient route for the synthesis of some novel aminopyrimidine, pyrazolo[1,5-*a*]pyrimidine, triazolo[1,5-*a*]pyrimidine, pyrimido[1,2-*a*]benzimidazole, and pyrido[2,3-*d*]pyrimidine derivatives. Some of the newly synthesized compounds were tested *in vitro* for their antibacterial and antifungal activities, and showed promising results.

INTRODUCTION

Enaminone derivatives have proven to be valuable synthons for the synthesis of a wide variety of biologically active heterocyclic systems.[1-3] On the other hand, many synthetically produced compounds containing the benzimidazole ring system are biologically active as fungicides[4] and as antihelmitic in veterinary medicine,[5,6] in addition to their wide pharmaceutical, medicinal and industrial applications.[7,8] As an extension of our efforts directed towards development of convenient synthetic approaches for the construction of biologically active heterocycles,[9-12] we accentuate the synthetic scope of *E*-1-(1-methylbenzimidazol-2-yl)-3-*N*,*N*-dimethylaminoprop-2-enone (**1**)[12] towards some nitrogen nucleophiles aiming at the synthesis of a variety of new heterocyclic compounds and to evaluate their biological activity.

RESULTS AND DISCUSSION

Treatment of the enaminone **1** with guanidine, resulted in the formation of a high yield of the 2-amino-4-(1-methylbenzimidazol-2-yl)pyrimidine (**3**) (Scheme 1).



Scheme 1

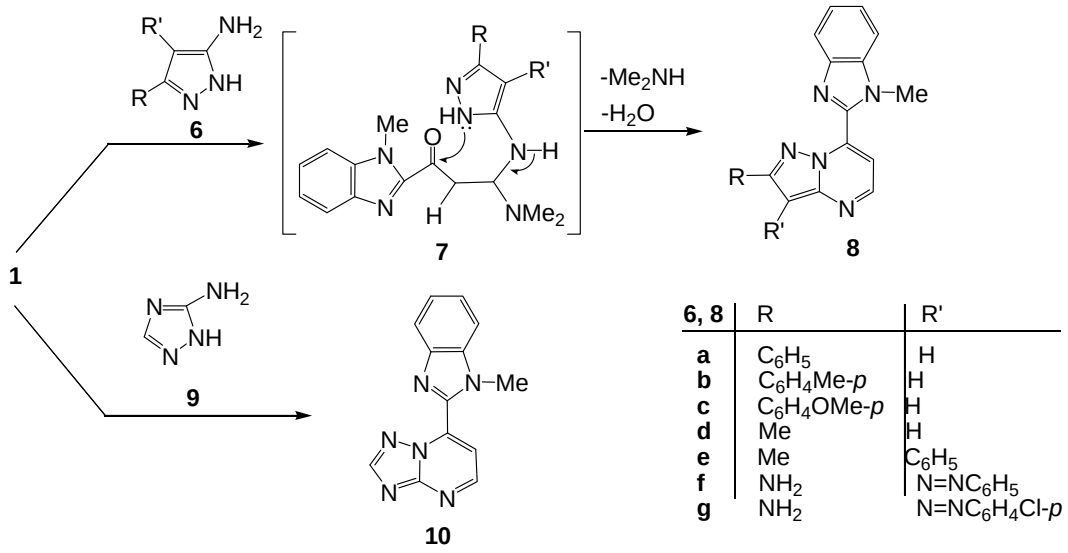
Structure **3** was assigned to the reaction product based on its elemental analysis and spectral data. For example, its IR spectrum showed two absorption bands at 3367 cm^{-1} and 3120 cm^{-1} due to a primary amino group. Its ^{1}H NMR spectrum of the same compound revealed a singlet signal at δ 4.28 due to N-CH_3 group, D_2O-exchangeable signal at δ 6.87 due to NH_2 protons, two doublet signals at δ 6.87 and 8.40 with *J* values 5.1 Hz due to pyrimidine protons and, in addition to an aromatic multiplet at δ 7.28-7.73. Compound **3** is assumed to be formed *via* an initial *Michael-type* addition of an amino group of guanidine to the activated double bond in the enaminone **1** followed by elimination of dimethylamine and water molecules from the intermediate **2** (Scheme 1).

Also, the enaminone **1** underwent cyclocondensation upon treatment with hydrazine to afford the not readily available 2-(*1H*-pyrazol-3-yl)-1-methylbenzimidazole (**5**) (Scheme 1). The IR spectrum of the latter product showed NH absorption band at 3132 cm^{-1}. Its ^{1}H NMR spectrum revealed a singlet signal at δ 4.21 due to N-CH_3 group, two doublet signals at δ 6.47 and 7.70 with *J* values 1.2 Hz due to pyrazole protons and D_2O-exchangeable signal at δ 12.81 due to NH proton, in addition to an aromatic multiplet at δ 7.42-7.55.

The behaviour of the enaminone **1** towards some aminopyrazole derivatives as potential precursors for interesting biologically active pyrazolo[1,5-*a*]pyrimidine derivatives[13] was also investigated. Thus, when the enaminone **1** was treated with 5-amino-1*H*-pyrazole derivatives **6a-g** in refluxing ethanol and in the presence of catalytic amount of piperidine, it afforded, the corresponding 7-(1-methylbenzimidazol-2-yl)-

pyrazolo[1,5-*a*]pyrimidine derivatives **8a-g** in almost quantitative yield (Scheme 2). The mass spectrum of compound **8a** taken as an example of the prepared series, revealed a molecular ion peak at *m/z* 325. Its ^{1}H NMR spectrum revealed a singlet signal at δ 7.06 (CH-3) and two doublet signals at δ 7.21, 8.61 (*J* = 4.2 Hz) due to pyrimidine protons (CH-6, CH-5), respectively, in addition to aromatic protons as a multiplet at δ 7.26-7.75. The singlet signal at δ 7.06 disappeared when 4-substiuted-5-aminopyrazole derivatives **6e-g** were used in the reaction. The IR spectrum of **8a** revealed the absence of any band due to carbonyl function.

The formation of the products **8a-g** is assumed to take place *via* an initial addition of the exocyclic amino group in the aminopyrazoles **6** to the α,β-unsaturated moiety in the enaminone **1** to yield the corresponding acyclic non-isolable intermediates **7a-g** which undergo intramolecular cyclization and aromatization to give the final products **8a-g** (Scheme 2).



6, 8	R	R'
a	C_6H_5	H
b	C_6H_4Me-*p*	H
c	C_6H_4OMe-*p*	H
d	Me	H
e	Me	C_6H_5
f	NH_2	$N{=}NC_6H_5$
g	NH_2	$N{=}NC_6H_4Cl$-*p*

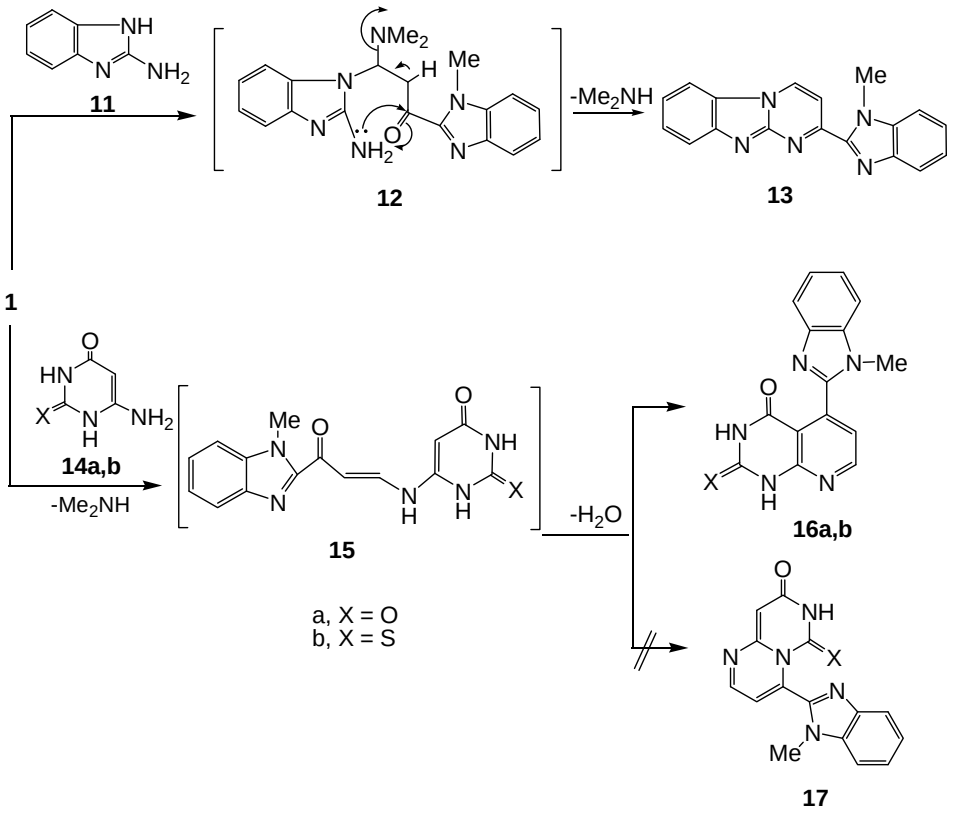
Scheme 2

Similarly, the enaminone **1** reacts with 3-amino-1,2,4-triazole (**9**) in refluxing pyridine to afford 7-(1-methylbenzimidazole-2-yl)-1,2,4-triazolo[1,5-*a*]pyrimidine (**10**) as shown in Scheme 2. The ^{1}H NMR spectrum of the latter product revealed a singlet signal at δ 8.60 (CH-2) and two doublet signals at δ 7.59 and 9.00 (*J* = 4.5 Hz) due to pyrimidine protons CH-6 and CH-5, respectively in addition to a multiplet at δ 7.26-7.75 due to aromatic protons. The IR spectrum of the same compound revealed the absence of absorption band due to carbonyl function.

In contrast to its behaviour towards the aminopyrazole derivatives **6a-g**, and the aminotriazole **9**, the enaminone **1** reacts with 2-aminobenzimidazole (**11**), in refluxing pyridine, to afforded only one isolable product (as examined by TLC). The reaction product was identified as 3-(1-methylbenz imidazol-2-yl)-pyrimido[1,2-*a*]benzimidazole (**13**) (Scheme 3). The IR spectrum of the latter product revealed no bands due to amino or carbonyl functions. Moreover, its ^{1}H NMR spectrum revealed an aromatic multiplet in

region δ 7.26-8.03 and one singlet signal at δ 4.26 due to the N-CH_3 protons, in addition to two doublets at δ 8.19 and 8.81 with *J* values = 7.2 Hz due to two protons of pyrimidine ring.

The formation of compound **13** is assumed to take place *via* addition of the imino function (endocyclic nitrogen) in compound **11** to the double bond in the enaminone **1** to give the acyclic non-isolable intermediate **12**. The latter product undergoes intramolecular cyclization and subsequent aromatization *via* the loss of dimethylamine and water molecules to afford the final product **13** (Scheme 3).



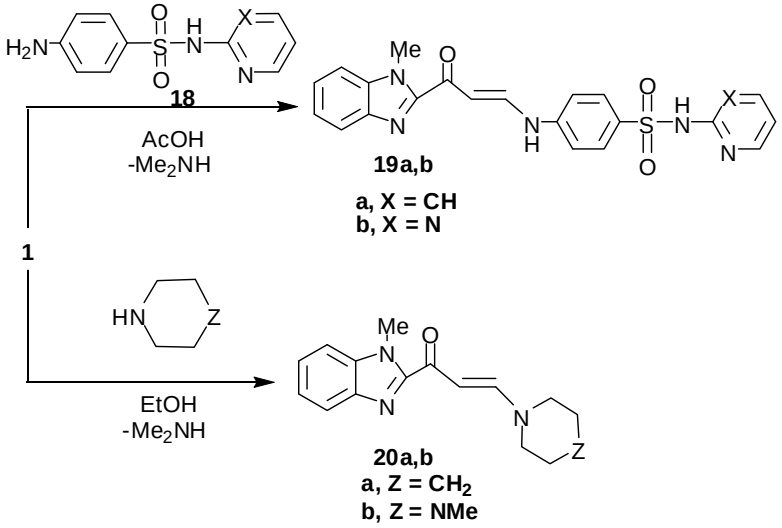
Scheme 3

When the enaminone **1** was treated with 6-amino-2,3-dihydro-*1H*-pyrimidin-4-one derivatives **14a**, **b**, in refluxing acetic acid, it afford the corresponding pyrido[2,3-*d*]pyrimidine derivatives **16a**, **b** (Scheme 3). The ^{1}H NMR spectrum of compound **16a** revealed four signals readily recognizable as two doublet signals at δ 8.15, 8.39 (*J* = 8.1 Hz) due to pyridine ring protons and two signals (D_2O-exchangeable) assigned to 2NH protons at δ 11.51 and 11.85, in addition to a multiplet at δ 7.26-7.75 due to aromatic protons. The IR spectra of compounds **16a**, **b** revealed, in each case, the absence of bands corresponding to an amino group. The formation of compounds **16a**, **b** can be explained on the basis of an initial addition of the amino group in aminopyrimidines **14a**, **b** to the double bond in enaminone **1** followed by elimination of dimethylamine to afford the non-isolable intermediates **15a**, **b**. The latter intermediates may be cyclize into the pyrido[2,3-*d*]pyrimidine derivatives **16a**, **b** or to pyrimido[1,6-*a*]pyrimidine **17**, respectively (Scheme 3). However, structure **17** is easily excluded on the basis of the spectral data of the

isolated products (*see Experimental*).

Treatment of enaminone **1** with sulphapyridine **18a** or sulphapyrimidine **18b**, in refluxing acetic acid, afforded the corresponding sulphonamide derivatives **19a** and **19b**, respectively in almost quantitative yields (Scheme 4). The IR spectra of reaction products showed, in each case, two absorption bands due to 2NH function in the region 3233-3105 cm^{-1} in addition to carbonyl absorption bands in the region 1643-1639 cm^{-1}. Their mass spectra showed, in each case, a peak corresponding to molecular ion. The ^1H NMR spectrum of compound **19a** revealed four signals readily recognizable as two doublet signals at δ 7.02, 8.22 (J = 13.2 Hz) due to the ethylenic protons, which indicated that it existed exclusively in the *E*-configuration, and two signals (D_2O-exchangeable) assigned to 2NH protons at δ 10.55, 10.60 in addition to aromatic protons as a multiplet in the region δ 6.64-8.03.

In a similar manner, the enaminone **1** reacts with piperidine and with 1-methylpiperazine in refluxing ethanol to give the corresponding tertiary amines **20a**, **b** (Scheme 4).



Scheme 4

The latter products are structurally related to some compounds recently identified as histamine H_4 receptor (H_4R) antagonists.[14]

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide disks on a pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. 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 chloroform ($CDCl_3$) or dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V.

Elemental analyses and the biological evaluation of the selected newly synthesized heterocyclic compounds were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

5-Amino-1*H*-pyrazole derivatives **6**[15-17] were prepared according to the reported literature.

2-Amino-4-(1-methylbenzimidazol-2-yl)pyrimidine (3)

A solution of guandine nitrate (1.73 g, 14.2 mmol) in absolute EtOH (15 mL) was added to a stirred solution of the *E*-1-(1-methylbenzimidazol-2-yl)-3-*N*,*N*-dimethylaminoprop-2-enone (**1**) (11.3 mmol) in boiling absolute EtOH (10 mL) and stirring was continued for 20 min. To this mixture, was added EtONa solution (22.6 mmol) in absolute EtOH (10 mL) and the reaction mixture was refluxed for 16 h. The solution was allowed to cool at rt and the precipitate was removed by filtration followed by concentration of filtrate under reduced pressure. The solid products that formed was collected by filtration, washed with water and dried. Recrystallization from DMF afforded the 2-amino-4-(1-methylbenzimidazol-2-yl)-pyrimidine (**3**) in 55g (90%). mp 272-274 ˚C; IR (KBr) υ_{max} /cm^{-1}: 3367, 3120 (NH_2), 1583 (C=N); ^{1}H NMR (DMSO-d_6): δ 4.28 (s, 3H, NCH_3), 6.87(s, 2H, NH_2), 6.88 (d, 1H, *J* = 5.1 Hz pyrimidine-5-CH), 7.28-7.73 (m, 4H, ArH's), 8.40 (d, 1H, *J* = 5.1 Hz pyrimidine-6-CH); MS (*m/z*): 225 (M^+, 100%). Anal. Calcd for $C_{12}H_{11}N_5$ (225.25): C, 63.99; H, 4.92; N, 31.09%. Found: C, 64.12; H, 4.81; N, 31.07%.

2-(1H-Pyrazol-3-yl)-1-methylbenzimidazole (5).

Hydrazine hydrate (2 mL, 100%) was added to a stirred solution of the enaminone **1** (2.29, 10 mmol) dissolved in AcOH (30 mL). Stirring was continued overnight at rt and the solid product obtained was filtered off, dried and recrystallized from EtOH to afford 2-(*1H*-pyrazol-3-yl)-1-methylbenzimidazole **(5)** g (76%); mp 180-182 ˚C; IR (KBr) υ_{max} /cm^{-1}: 3132 (NH), 1597 (C=N); ^{1}H NMR (DMSO-d_6): δ 4.21 (s, 3H, NCH_3), 6.46 (d, 1H, *J* = 1.2 Hz pyrazole-4-CH), 7.42-7.55 (m, 4H, ArH's), 7.70 (d, 1H, *J* = 1.2 Hz pyrazole-5-CH), 12.81 (s, 1H, NH, D_2O-exchangable); MS (*m/z*): 198 (M^+, 100%), 92 (30.2%). Anal. Calcd for $C_{11}H_{10}N_4$ (198.22): C, 66.65; H, 5.09; N, 28.26%. Found: C, 66.80; H, 5.01; N, 28.19%.

7-(1-Methylbenzimidazol-2-yl)pyrazolo[1,5-a]pyrimidine derivatives 8a-g

General procedure.

To a mixture of *E*-1-(1-methylbenzimidazol-2-yl)-3-*N*,*N*-dimethylaminoprop-2-enone **(1)** (2.29 g, 10 mmol) and the appropriate aminopyrazole derivative **6a-g** (10 mmol), in absolute EtOH (25 mL), a few drops of piperidine was added and the reaction mixture was refluxed for 3h. The solid product was filtered off, washed with EtOH and recrystallized from EtOH/DMF to afford the pyrazolo[1,5-*a*]pyrimidine derivatives **8a-g** in 65-70% yield.

7-(1-Methylbenzimidazol-2-yl)-2-phenylpyrazolo[1,5-a]pyrimidine 8a

Yield (70%); mp 248-249 ˚C; IR (KBr) υ 1596 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.91 (s, 3H, NCH_3), 7.06 (s, 1H, pyrazole-3-CH), 7.20 (d, 1H, *J* = 4.2 Hz pyrimidine-6-CH), 7.26-7.75 (m, 9H, ArH's), 8.61 (d, 1H, *J* = 4.2 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d_6) δ 31.58, 93.99, 110.01, 111.23, 119.85, 122.63, 123.87, 126.17, 128.76, 129.21, 131.99, 136.11, 136.38, 142.49, 144.68, 149.58, 150.59, 155.45; MS *m/z* (%) 325 (M^+, 100), 297 (34.9), 195 (10.9), 77 (36.2). Anal. Calcd for $C_{20}H_{15}N_5$: C, 73.83; H, 4.65; N, 21.52%. Found: C, 73.92; H, 4.52; N, 21.56%.

7-(1-Methylbenzimidazol-2-yl)-2-(4-methylphenyl)pyrazolo[1,5-a] pyrimidine 8b

Yield (70%); mp 242-244 ˚C; IR (KBr) υ 1594 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.61 (s, 3H, CH_3), 4.01 (s, 3H, NCH_3), 7.16 (d, 1H, *J*= 4.9 Hz pyrimidine-6-CH), 7.29 (s, 1H, pyrazole-3-CH), 7.36-7.81 (m, 8H, ArH's), 8.82 (d, 1H, *J*= 4.9 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d_6) δ 20.91, 31.73, 93.78, 111.13, 111.26, 119.94, 122.73, 123.96, 126.18, 129.28, 129.46, 136.17, 136.36, 138.84, 142.52, 144.15, 149.41, 150.07, 155.57; MS *m/z* (%) 339 (M^+, 100), 311 (33.9), 195 (12.9). Anal. Calcd for $C_{21}H_{17}N_5$: C, 74.32; H, 5.05; N, 20.63%. Found: C, 74.18; H, 5.12; N, 20.70%

2-(4-Methoxyphenyl)-7-(1-methylbenzimidazol-2-yl)pyrazolo[1,5-a] pyrimidine 8c

Yield (68%); mp 251-252 ˚C; IR (KBr) υ 1596 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.85 (s, 3H, N-CH_3), 3.93 (s, 3H, OCH_3), 6.96 (d, 1H, *J* = 5.1 Hz pyrimidine-6-CH), 7.29 (s, 1H, pyrazole-3-CH), 7.36-7.81 (m, 8H, ArH's), 8.56 (d, 1H, *J* = 5.1 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d_6) δ 31.68, 55.17, 93.29, 110.92, 111.04, 114.24, 119.89, 122.64, 123.86, 124.52, 127.64, 136.13, 136.26, 142.50, 144.47, 149.24, 150.08, 155.42, 160.12; MS *m/z* (%) 355 (M^+, 100%), 195 (16.9%). Anal. Calcd for $C_{21}H_{17}N_5O$: C, 70.97; H, 4.82; N, 19.71%. Found: C, 70.92; H, 4.72; N, 19.86%.

2-Methyl-7-(1-methylbenzimidazol-2-yl)pyrazolo[1,5-a]pyrimidine 8d

Yield (69%); mp 221 ˚C; IR (KBr) υ 1589 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.45 (s, 3H, CH_3), 3.84 (s, 3H, NCH_3), 7.05 (d, 1H, *J* = 4.3 Hz pyrimidine-6-CH), 7.19 (s, 1H, pyrazole-3-CH), 7.56-7.95 (m, 8H, ArH's), 8.61 (d, 1H, *J* = 4.3 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d_6) δ 10.63, 31.94, 91.95, 110.92, 111.04, 114.24, 119.89, 122.64, 123.86, 124.52, 127.64, 136.13, 136.26, 142.50, 144.47, 149.24, 150.08, 155.42, 160.12; MS *m/z* (%)263 (M^+, 100%), 195 (16.9%). Anal. Calcd for $C_{15}H_{13}N_5$: C, 68.42; H, 4.98; N, 26.60%. Found: C, 68.55; H, 4.80; N, 26.65%.

2-Methyl-7-(1-methylbenzimidazol-2-yl)-3-phenylpyrazolo[1,5-a] pyrimidine 8e

Yield (65%); mp 188-190 ˚C; IR (KBr) υ 1594 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.62 (s, 3H, CH_3), 3.84 (s, 3H, NCH_3), 7.21(d, 1H, *J* = 4.2 Hz pyrimidine-6-CH), 7.34-7.92 (m, 9H, ArH's), 8.61 (d, 1H, *J* = 4.2 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d_6) δ13.88, 31.26, 100.09, 110.79, 119.76, 122.47, 123.71,

126.19, 128.22, 128.49, 131.51, 135.89, 135.99, 142.41, 145.99, 149.16, 151.97; MS *m/z* (%) 339 (M^+, 100%), 311 (53.9%), 195 (11.9%), 77 (32%). Anal. Calcd for $C_{21}H_{17}N_5$: C, 74.32; H, 5.05; N, 20.63%. Found: C, 74.45; H, 5.00; N, 20.55%.

2-Amino-7-(1-methylbenzimidazol-2-yl)-3-phenylazopyrazolo[1,5-a] pyrimidine 8f

Yield (66%); mp 289-290 ˚C; IR (KBr) υ 3398, 3277 (NH_2), 1588 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3H, NCH_3), 4.78 (br. s, 2H, NH_2, D_2O exchangeable), 7.26 (d, 1H, *J* = 4.2 Hz pyrimidine-6-CH), 7.41-7.93 (m, 9H, ArH's), 8.21 (d, 1H, *J* = 4.2 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d_6) δ 32.89, 100.11, 108.40, 110.87, 119.72, 120.99, 122.72, 123.97, 128.54, 128.96, 135.56, 140.49, 141.98, 152.97. 153.29; MS *m/z* (%) 368 (M^+, 100%), 291 (37.9%), 169 (95.4%), 77 (46.1%). Anal. Calcd for $C_{20}H_{16}N_8$: C, 65.21; H, 4.38; N, 30.42%. Found: C, 65.41; H, 4.28;
N, 30.32%.

2-Amino-3-(4-chlorophenylazo)-7-(1-methylbenzimidazol-2-yl)pyrazolo-[1,5-a]pyrimidine 8g

Yield (68%); mp 275-276 ˚C; IR (KBr) υ 3408, 3297 (NH_2), 1588 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.99 (s, 3H, NCH_3), 5.03 (br. s, 2H, NH_2, D_2O exchangeable), 7.16 (d, 1H, *J* = 4.2 Hz pyrimidine-6-CH), 7.29-7.81 (m, 8H, ArH's), 8.09 (d, 1H, *J* = 4.2 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d_6) δ 31.41, 110.84, 111.82, 114.89, 119.88, 122.65, 122.73, 123.91, 129.11, 132.78, 135.91, 135.93, 142.46, 143.81, 147.21, 150.54, 151.65, 152.35; MS *m/z* (%) 402 (M^+, 100%), 169 (25.4%), 77 (16.1%). Anal. Calcd for $C_{20}H_{15}ClN_8$: C, 59.63; H, 3.75; N, 27.82%. Found: C, 59.73; H, 3.80; N, 27.67%.

Synthesis of triazolo[1,5-a]pyrimidine and pyrimido[1,2-a]benzimidazole derivatives 10 and 13.

General procedure.

To a mixture of *E*-1-(1-methylbenzimidazol-2-yl)-3-*N*,*N*-dimethylaminoprop-2-enone (**1**) (2.29 g, 10 mmol) and the appropriate heterocyclic amine (3-amino-l,2,4-triazole (**9**), 2-aminobenzimidazole (**11**)) (10 mmol) in pyridine (25 mL) was refluxed for 12 h, then left to cool. The solvent was evaporated in *vacuo* and the residual solid was taken in EtOH then collected by filtration, washed with water, dried and finally recrystallized from DMF/H_2O to afford the corresponding triazolo[1,5-*a*]pyrimidine and pyrimido[1,2-*a*]benzimidazole derivatives **10** and **13**, respectively. The physical and spectral data of the synthesized compounds **10** and **13** are listed below.

7-(1-Methylbenzimidazol-2-yl)-1,2,4-triazolo[1,5-a]pyrimidine 10

Yield (84%); mp 228 ˚C; IR (KBr) υ 1611 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3H, NCH3), 7.25-7.75 (m, 4H, ArH's and 1H pyrimidine-6-CH), 8.60 (s, 1H, triazole-2-CH), 9.00 (d, 1H, *J* = 4.5 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d_6) δ 31.67, 111.10, 113.235, 120.01, 122.89, 124.19, 136.15,

138.07, 142.43, 143.06, 155.13, 155.96; MS *m/z* (%) 250 (M^+, 100%), 196 (54.4%), 77 (31.5.1%). Anal. Calcd for $C_{13}H_{10}N_6$: C, 62.39; H, 4.03; N, 33.58%. Found: C, 62.50; H, 3.93; N, 33.57%.

3-(1-Methylbenzimidazol-2-yl)pyrimido[1,2-a]benzimidazole 13

Yield (81%); mp > 300 ˚C; IR (KBr) υ 1620 (C=N) cm–1; ^{1}H NMR (DMSO-d_6) δ 4.25 (s, 3H, NCH3), 7.25-8.03 (m, 8H, ArH's), 8.18 (d, 1H, *J* = 7.2 Hz pyrimidine-2-CH), 8.81 (d, 1H, *J* = 7.2 Hz pyrimidine-1-CH); ^{13}C NMR (DMSO-d_6) δ 33.17, 106.11, 111.17, 112.53, 119.17, 120.04, 121.89, 122.98, 124.48, 126.23, 135.89, 137.57, 141.23, 150.52, 164.28; MS *m/z* (%) 299 (M^+, 100%), 150 (11.6%), 102 (12.9%). Anal. Calcd for $C_{18}H_{13}N_5$: C, 72.22; H, 4.38; N, 23.40%. Found: C, 72.32; H, 4.29; N, 23.39%.

Synthesis of pyrido[2,3-d]pyrimidine derivatives 16a, b

General procedure.

A mixture of the enaminone **1** (2.29 g, 10 mmol) and the appropriate aminopyrimidine derivative **14a**, **b** (10 mmol) in AcOH (25 mL) was refluxed for 8 h, then left to cool. The reaction mixture was poured into cold water and the solid product was filtered off, washed with water, dried and finally recrystallized from DMF/H_2O to afford the corresponding pyrido[2,3-*d*]pyrimidine derivatives **16a**, **b**.

5-(1-Methylbenzimidazol-2-yl)-1H,3H-pyrido[2,3-d]pyrimidine-2,4-dione 16a.

Yield (74%); mp >300 ˚C; IR (KBr) υ 3156 (NH), 1709 (CO), 1606 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.30 (s, 3H, NCH_3), 7.26-7.75 (m, 4H, ArH's), 8.15 (d, 1H, pyridine-6-CH, *J* = 8.1 Hz), 8.39 (d, 1H, pyridine-7-CH, *J* = 8.1 Hz), 11.51 (br. s, 1H, NH, D_2O-exchangeable), 11.85 (br. s, 1H, NH, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6) δ 33.07, 109.33, 110.96, 118.43, 119.73, 122.67, 123.79, 137,028, 137.31, 141.93, 147.86, 150.49, 151.55, 153.56, 161.98; MS *m/z* (%) 293 (M^+, 100%), 131 (18.5), 77 (17.6%). Anal. Calcd for $C_{15}H_{11}N_5O_2$: C, 61.43; H, 3.78; N, 23.88%. Found: C, 61.62; H, 3.60; N, 23.87%.

5-(1-Methylbenzimidazol-2-yl)-2-thioxo-2,3-dihydro-1H-pyrido[2,3-d] pyrimidin-4-one 16b.

Yield (70%); mp >300 ˚C; IR (KBr) υ 3115 (NH), 1681 (CO), 1606 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.28 (s, 3H, NCH_3), 7.27-7.91 (m, 4H, ArH's), 8.23 (d, 1H, pyridine-6-CH, *J* = 8.1 Hz), 8.38 (d, 1H, pyridine-7-CH, *J* = 8.1 Hz), 12.65 (br. s, 1H, NH, D_2O-exchangeable), 13.30 (br. s, 1H, NH, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6) δ 33.19, 111.06, 111.40, 119.82, 122.79, 123.98, 136.93, 137.39, 141.95, 147.59, 150.76, 153.86, 159.40, 176.05; MS *m/z* (%) 309 (M^+, 100%), 131 (22.2%), 77 (15.2%). Anal. Calcd for $C_{15}H_{11}N_5OS$: C, 57.86; H, 4.21; N, 22.49; S, 10.30%. Found: C, 57.96; H, 4.30; N, 22.36; S, 10.24%.

Synthesis of sulfonamide derivatives 19a, b

General procedure.

A mixture of *E*-1-(1-methylbenzimidazol-2-yl)-3-*N,N*-dimethylaminoprop-2-enone (**1**) (5 mmol) and sulphapyridine (**18a**) or sulphapyrimidine (**18b**) (5 mmol) in AcOH (20 mL) was refluxed for 2 h, then allowed to cool. The precipitated product was collected by filtration, washed with ethanol and dried. Recrystallization from DMF/H_2O afforded sulfonamide derivatives **19a** and **19b**, respectively.

4-[3-(1-Methylbenzimidazol-2-yl)-3-oxo-propenylamino]-N-pyridin-2-yl-benzenesulfonamide 19a.

Yield (74%); mp 268-270 ˚C; IR (KBr) υ 3225, 3115(2NH), 1648 (C=O), 1593 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.18 (s, 3H, NCH_3), 6.64-8.03 (m, 13H, 12H ArH's, 1H, -CO-CH=), 8.21 (J = 13.2 Hz, 1H, =CH-N), 10.55 (br. s, 1H, NH, D_2O exchangeable), 10.59 (br. s, 1H, NH, D2O exchangeable); ^{13}C NMR (DMSO-d_6) δ 32.08, 97.31, 111.10, 113.54, 115.30, 115.95, 116.25, 116.87, 122.89, 123.02, 128.55, 128.78, 130.22, 134.72, 136.79, 140.05, 141,18, 144.15, 145.06, 147.91, 152.94, 189.13; MS *m/z* (%) 433 (M^+, 100%), 248 (13.5%), 77 (5.5%). Anal. Calcd for $C_{22}H_{19}N_5O_3S$: C, 60.96; H, 4.42; N, 16.16; S, 7.40 %. Found: C, 61.12; H, 4.45; N, 16.10; S, 7.27 %.

4-[3-(1-Methylbenzimidazol-2-yl)-3-oxopropenylamino]-N-pyrimidin-2-ylbenzenesulfonamide 19b.

Yield (77%); mp 280-282 ˚C; IR (KBr) υ 3233, 3105 (2NH), 1649 (C=O), 1578 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.13 (s, 3H, NCH_3), 6.87-8.01 (m, 12H, 11H ArH's, 1H, -CO-CH=), 8.27 (d, 1H, J = 13.2 Hz, =CH-N), 10.52 (br. s, 1H, NH, D_2O-exchangeable), 11.26 (br. s, 1H, NH, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6) δ 32.24, 97.55, 111.05, 115.07, 115.81, 116.00, 116.66, 123.03, 123.16, 124.67, 124.78, 129.89, 133.06, 136.77, 141.17, 143,16, 147.85, 157.04, 158.36, 163.16, 189.19; MS *m/z* (%) 434 (M^+, 100%), 250 (19.9 %), 77(10.5%). Anal. Calcd for $C_{21}H_{18}N_6O_3S$: C, 58.05; H, 4.18; N, 19.34; S, 7.38 %. Found: C, 58.28; H, 4.03; N, 19.30; S, 7.34 %.

Reaction of E-1-(1-methylbenzimidazol-2-yl)-3-N,N-dimethylaminoprop-2-enone (1) with piperidine, and with 1-methylpiperazine.

General procedure.

A mixture of *E*-1-(1-methylbenzimidazol-2-yl)-3-*N,N*-dimethylaminoprop-2-enone (**1**) (5 mmol) and piperidine or 1-methylpiperazine (3 mL) in EtOH (30 mL) was refluxed for 10 h, then allowed to cool. The precipitated product was collected by filtration, washed with EtOH and dried. Recrystallization from EtOH/DMF afforded **20a** and **20b,** respectively.

1-(1-Methylbenzimidazol-2-yl)-3-piperidin-1-ylprop-2-en-1-one 20a.

Yield (77%); mp 220-222 ˚C; IR (KBr) υ 1639 (C=O), 1598 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ

2.11-2.25 (m, 6H, piperidine), 3.22-3.39 (m, 4H, piperidine), 4.46 (s, 3H, NCH3), 7.31-8.30 (m, 5H, 4H ArH's, 1H, -CO-CH=), 8.74 (d, 1H, *J* = 12.2 Hz, 1H, =CH-N); ^{13}C NMR (DMSO-d_6) δ 23.37, 24.63, 26.22, 31.82, 45.99, 54.28, 92.53, 110.71, 122.45, 123.70, 136.55, 141.12, 149.03, 152.46, 179.65; MS *m/z* (%) 269 (M^+, 100%). Anal. Calcd for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60 %. Found: C, 71.25; H, 7.26; N, 15.55 %.

1-(1-Methylbenzimidazol-2-yl)-3-(4-methylpiperazin-1-yl)prop-2-en-1-one 20b.

Yield (80%); mp 187-189 ˚C; IR (KBr) υ 1643 (C=O), 1588 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 3H, CH_3), 2.37-2.40 (m, 4H, piperazine) 3.45-3.50 (m, 4H, piperazine), 4.51 (s, 3H, NCH_3), 7.02-7.71 (m, 5H, 4H ArH's, 1H, -CO-CH=), 8.74 (d, 1H, *J* = 12.7 Hz, 1H, =CH-N); ^{13}C NMR (DMSO-d_6) δ 30.9, 40.99, 49.23, 52.66, 56.85, 57.54, 92.65, 111.25, 112.01, 122.49, 123.61, 136.21, 140.23, 145.69, 154.33, 181.12; MS *m/z* (%) 284 (M^+, 100%). Anal. Calcd for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09; N, 19.70 %. Found: C, 67.66; H, 7.05; N, 19.66 %.

BIOLOGICAL ACTIVITY

The antibacterial and antifungal activity were carried out in the Microbiology Division of Microanalytical Center of Cairo university, using the diffusion plate method[18-20] a bottomless cylinder containing a measured quantity (1ml, mg/mL) of the sample is placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar broth) or fungal medium (Dox's medium) which has been heavily seeded with the spore suspention of the test organism. After incubation (24 h for bacteria and 5 days for fungi), the diameter of the clear zone of inhibition surrounding the sample is taken as measure of the inhibitory power of the sample agaist the particular test organism.

Most of the compounds were tested *in vitro* against gram negative bacteria [*Escherichia coli* anaerobic (EC) and Neisseria gonorrheae (NG)], gram positive bacteria [*Bacillus subtilis* (BS), *Staphylococcus albus* (SA) and *Enterococcus faecalis* (EF)] and antifungal activity against *Candida albicans* (CA). The reference antibiotics *Ampicillin and Tetracycline* were used as references to evaluate the potency of the tested compounds under the same condition. The test results are depicted in Table 1 on the following basis:

The solvent used was ethanol.

Concentration of the sample in 100 µg/ml.

IZD = 2-10 mm beyond control = + (low activity).

IZD = 11-24 mm beyond control = ++ (moderate activity).

IZD = 25-35 mm beyond control = +++ (high activity).

Table 1. Antibacterial and Antifungal Activities of the Synthesized Compounds

Compound No.	Inhibition Zone Diameter (IZD) (mm/mg Compound Tested)					
	Gram (-)			Gram (+)		Fungi
	(EC) anaerobic	(NG)	(BS)	(SA)	(EF)	(CA)
Control	0.0	0.0	0.0	0.0	0.0	0.0
3	16 ++	20 ++	15 ++	16 ++	22 ++	13 ++
8a	14 ++	20 ++	17 ++	19 ++	18 ++	16 ++
8b	18 ++	15 ++	12 ++	16 ++	16 ++	17 ++
8d	15 ++	15 ++	12 ++	15 ++	20 ++	12 ++
8f	15 ++	13 ++	14 ++	15 ++	19 ++	13 ++
8g	16 ++	12 ++	13 ++	14 ++	16 ++	15 ++
10	20 ++	16 ++	13 ++	17 ++	21 ++	20 ++
13	13 ++	13 ++	15 ++	13 ++	20 ++	13 ++
16a	15 ++	12 ++	10 +	16 ++	17 ++	15 ++
19a	13 ++	12 ++	15 ++	13 ++	18 ++	14 ++
19b	17 ++	12 ++	13 ++	13 ++	17 ++	14 ++
20a	20 ++	15 ++	13 ++	19 ++	18 ++	13 ++
Ampicillin	**35** +++	**26** +++	**33** +++	**34** +++	**35** +++	**20** ++
Tetracycline	**31** +++	**25** +++	**30** +++	**27** +++	**31** +++	**27** +++

The test results revealed that all compounds exhibited moderate activity against five bacterial species, *Candida albicans* (CA) except compound **16a** exhibited low activity against *Bacillus subtilis* (BS).

REFERENCES

1. J. V. Greenhill, *Chem. Soc. Rev.*, 1977, **6**, 277.
2. E. Bejan, H. A. Haddou, J. C. Daran, and G. G. A. Balavoine, *Synthesis*, 1996, 1012.
3. B. Stanovnik and J. Svete, *Chem. Rev.*, 2004, **104**, 2433.
4. A. N. Dhage, N. S. Joshi, S. G. Wadokar, and A. V. Kasture, *Indian Drugs*, 1986, **23**, 601. [*Chem.*

Abstr., 106, 168513f (1987)].

5. M. Gbadamassi, J. L. Barascut, J. L. Imbach, and P. Gayral, *Eur. J. Med. Chem.*, 1988, **23**, 225.
6. P. N. Preston, *Chem. Rev.,* 1974, **74**, 279.
7. A. M Farag, *J. Chem. Res. (S),* 1994, 432.
8. A. M. A. Meziane, M. Rahmouni, J. P. Bazureau, and J. Hamelin, *Synthesis,* 1998, 967.
9. K. M. Dawood, E. A. Ragab, and A. M. Farag, *J. Chem. Res. (S),* 2003, 685. (M) 2003, 1151.
10. A. M Farag, K. M. Dawood, and H. A. El-menoufy, *Heteroatom Chem.*, 2004, **15**, 508.
11. Y. M. Elkholy, K. A. Ali, and A. M. Farag, *Letters in Organic Chemistry,* 2006, **3**, 195.
12. R. M. Shaaban, T. S. Saleh, Faiz Osman, andA. M. Farag, *J. Heterocycl. Chem.,* 2007, **44**, 177.
13. T. Novinson, R. M. Dimmitt, L. N. Simon, R. K. Robins, and D. E. Brien, *J. Med. Chem.,* 1974, **17**, 645.
14. N. Terzioglu, R. M. V. Rijn, R. A. Bakker, I. J. P. Esch, and R. Leurs, *Bioorg. Med. Chem. Lett.,* 2004, **14**, 5251.
15. A. Takamizawa and Y. Hamashima,*Yakugaku Zasshi,* 1964, **84**, 1113.
16. M. H. Elnagdi, H. A. Elfahham, S. A. S. Ghozlan, and G. E. Elgemeie, *J. Chem. Soc., Perkin Trans.1,* 1982, 2663.
17. M. H. Elnagdi, E. M. Kandeel, E. M. Zayed, and Z. E. Kandeel, *J. Heterocycl. Chem.,* 1977, **14**, 155.
18. D. N. Muanz, B. W. Kim, K. L. Euler, and L. William, *Int. J. Pharmacog.,* 1994, **32**, 337.
19. R. J. Grager and J. B. Harbone, *Phytochemistry,* 1994, **37**, 19.
20. O. N. Irab, M. M. Young, and W. A. Anderson, *Int. J. Pharmacog.,* 1996, **34**, 87.