Microwave Mediated Facile Synthesis of Some Novel Pyrazole, Pyrimidine, Pyrazolo[1,5-a]pyrimidine, Triazolo[1,5-a]pyrimidine and Pyrimido[1,2-a] benzimidazole Derivatives Under Solventless Condition

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Abstract: Ssynthesis of some new pyrazole, pyrimidine, pyrazolo[1,5-a]pyrimidine, triazolo[1,5-a]pyrimidine and pyrimido[1,2-a]benzimidazole derivatives using E-1-(4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3-(dimethylamino)prop-2-ene-1-one as building block *via* solventless reaction system under microwave irradiations or in presence of solvent under reflux conditions were undertaken. In general improvement in yields and reduction of the reaction time were observed when the reactions were carried out under microwave irradiation compared with classical method.

[El-Kateb, A.A.; Abd El-Rahman, N.M.; Saleh, T.S. ; Ali, M. Hassan; Elhaddad, A. S. and El-Dosoky, A.Y. . **Microwave Mediated Facile Synthesis of Some Novel Pyrazole, Pyrimidine, Pyrazolo[1,5-a]pyrimidine, Triazolo[1,5-a]pyrimidine and Pyrimido[1,2-a] benzimidazole Derivatives Under Solventless Condition**. *Nat Sci* 2012;10(11):77-86]. (ISSN: 1545-0740). http://www.sciencepub.net/nature. 12

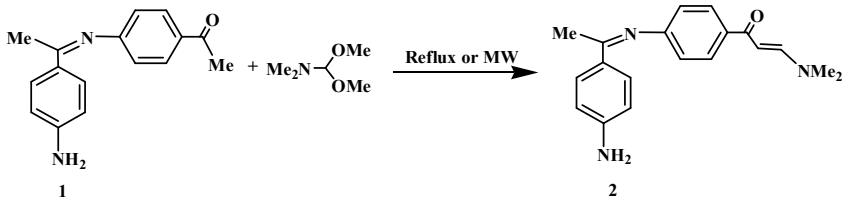
Keywords: Microwave, solventless, enaminone, pyrazole, pyrimidine, benzimidazole

1. Introduction

In the last few years, microwave-induced organic reaction enhancement (MORE) has gained popularity as a non-conventional technique for rapid organic synthesis[1] and many researchers have described accelerated organic reactions, with a large number of papers that have appeared proving the synthesis utility of MORE chemistry in routine organic synthesis.[2,3] It can be termed as 'e-chemistry' because it is easy, effective, economical, and eco-friendly, and is believed to be a step toward achieving green chemistry objectives.

Enaminone derivatives have proven to be valuable synthons for the synthesis of a wide variety of biologically active heterocyclic systems.[4-6] On the other hand Pyrazole and pyrimidine derivatives attracted the interest of organic chemists due to their biological and chemotherapeutic importance. Pyrazolopyrimidines and related fused heterocycles are potential bioactive molecules. They are known to exhibit pharmacological activities such as CNS depressant, [7,8] neuroleptic,[9] and tuberculostatic.[10] they are also identified as a general class of adenosine receptors. [11,12] in continuation of our interest of in the synthesis of varieties of heterocyclic systems for biological screening [13,14] in our present work we have synthesized some new pyrazole, pyrimidine, pyrazolo[1,5-a]pyrimidine, triazolo[1,5-a]pyrimidine and pyrimido[1,2-a]benzimidazole derivatives using enaminone **2** as building block *via* solvent-free reaction system under microwave irradiations or in presence of solvent under reflux conditions.

2. Result and Discussion:



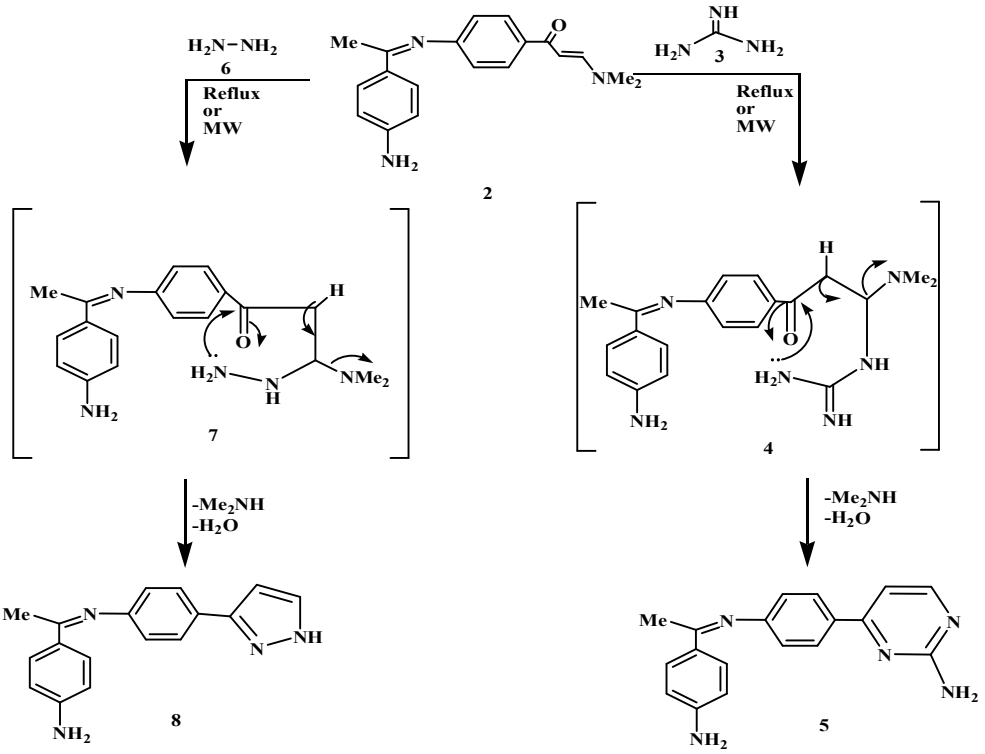
1 2

Scheme 1

The reaction of E-1-(4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3 (dimethylamino) prop -2-ene-1-one (**2**) with guanidine (**3**), under microwave irradiation in the presence of sodium carbonate or in refluxing ethanol (in the presence of two equivalent of sodium ethoxide, [15]) resulted in the formation of N(1-(4-aminophenyl)ethylidene)-4-(-2-aminopyrimidin-4-yl)benzenamine (**5**) in high yield (scheme 2).Structure **5** is assigned based on the elemental analyses and spectral data of the reaction product. For example its IR spectrum showed two asymmetric absorption bands at 3287, 3307 cm^{-1} due to the NH_2 group of aminobenzene, two asymmetric absorption bands at

3340, 3390 due to the NH_2 group of aminopyrimidine and two bands at 1540,1595cm^{-1} due to two C=N groups. its mass spectrum revealed a molecular ion peak at *m/z* 304, The ^{1}H NMR spectrum of the same compound revealed singlet signal at δ 2.06 due to methyl protons(CH_3-C=N-), two doublet signals at δ 6.88, 8.40 due pyrimidine protons and a D_2O-exchangeable two signals at δ 4.31, 10.09 due to NH_2 protons. A plausible mechanism for the formation of compound **5** is outlined in Scheme 2. It is assumed to be formed *via* an initial *Michael-type* addition of an amino group of guanidine to the activated double bond in enaminone **2** followed by elimination of dimethylamine and water molecules from the intermediate **4**

Also, enaminone **2** underwent cyclocondensation on treatment with hydrazine hydrate (**6**) to afford 4-(1-(4-(1H-pyrazol-5-yl)phenylimino)ethyl)benzenamine (**8**) (Scheme 1). the IR spectrum of compound **8**, showed NH absorption band at 3328 cm^{-1}, two asymmetric absorption bands at 3187, 3220 cm^{-1} due to the NH_2 group and two bands at 1545, 1595cm^{-1} due to C=N groups. The ^{1}H NMR spectrum of the same compound revealed singlet signal at δ 2.03 due to methyl protons (CH_3-C=N-), two doublet signals at δ 6.62, 7.70 due to pyrazole protons and D_2O-exchangeable signals at δ 9.97, 12.81 due to $NH_2$and NH protons. (*Cf. experimental part*).



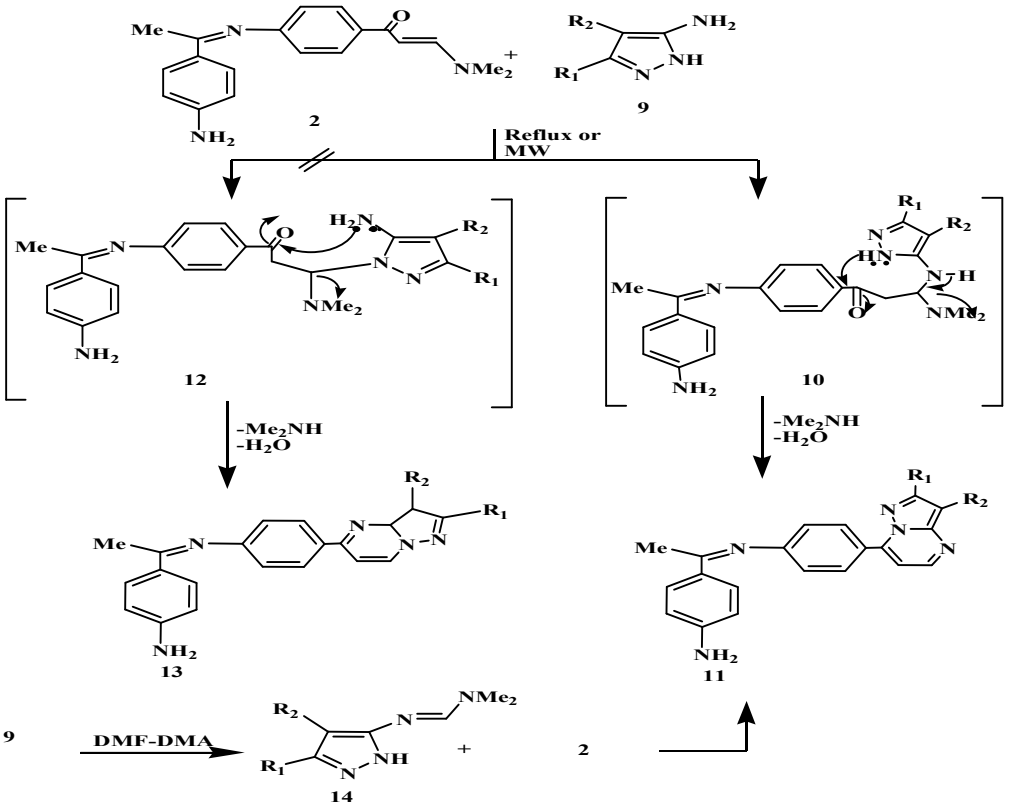
Scheme 2

The behaviour of E-1-(4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3-(dimethylamino)prop-2-ene-1-one (**2)** towards some aminopyrazole derivatives as potential precursors for interesting biologically active pyrazolo[1,5-*a*]pyrimidine derivatives[16] was also investigated. Thus, when enaminone **2** was treated with substituted 5-amino-1*H*-pyrazole derivatives (**9a-e)** under microwave irradiation in the presence of catalytic amount of piperidine or in refluxing ethanol in the presence of catalytic amount of piperidine, it afforded, the corresponding N-(1-(4-aminophenyl)ethylidene)-4-(substitutedpyrazolo[1,5-a]pyrimidin -7-yl)benzenamine derivative (**11a-k**) in almost quantitative yield (table 2) (Scheme 3).

Structures of compounds **11a-k** were established on the basis of their elemental analyses and spectral data. The IR spectrum revealed an absence of any band due to carbonyl group. Taken compound **11a** as representative example its mass spectrum revealed a molecular ion peak at m/z 405. Its ^{1}H NMR spectrum revealed singlet signal at δ 2.07 due to methyl protons (CH_3-C=N-), singlet signal at δ 7.28 due to pyrazole, two doublet signals at δ 7.22, 8.55 due to pyrimidine protons, singlet signal at 10.27 due to NH_2 group in addition to aromatic

protons as a multiplet at δ 7.33-8.28. The singlet signal at δ 7.28 due to pyrazole disappeared when compounds **9e-k** was used instead of compound **9a.**

The formation of products (**11a-k**) are assumed to take place via an initial Michael addition of the exocyclic amino group in the aminopyrazole **9a-k** to the α,β-unsaturated moiety in the enaminone **2** to yield the corresponding acyclic non-isolable intermediates (**10a-k**) which undergo cyclization and aromatization into the final products (**11a-k**) (Scheme 3). Although spectral data seemed of no help in distinguishing between the two structures **11** and **13**, structure **11** was firmly established for the reaction products by the synthesis of the same products via condensing **9** with dimethylformamidedimethylacetal (DMF-DMA) and subsequent condensation of so formed enaminone derivatives **14**[17] with 1(4-(1-(4-aminophenyl)ethylideneamino)phenyl)ethanone (**1**) to afford products identical in the all respects (m.p., mixed m.p. and comparative IR) with those corresponding structure **11** (Scheme 3).

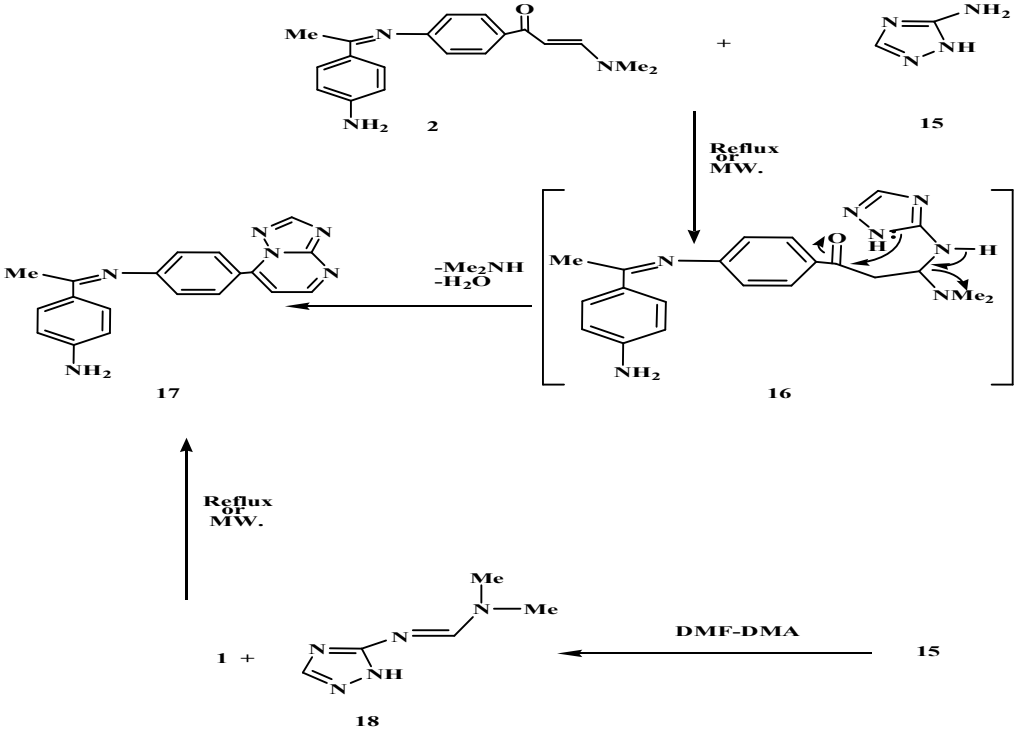


Scheme 3

Table 1 reaction of enaminone 2 with substituted 5-amino-1*H*-pyrazole derivatives (9a-k)

Product	R^1	R^2	Reflux		Microwave	
			Time (h)	Yield (%)	Time (min.)	Yield (%)
11 a	C_6H_5	H	7	55	7	85
11b	C_6H_4Cl-p	H	7	53	7	87
11 c	$C_6H_4OCH_3$-p	H	7	63	6	87
11 d	CH_3	H	7	55	7	88
11 e	CH_3	C_6H_5	7	57	10	90
11 f	NH_2	-N=N-Ph	5	63	5	90
11g	NH_2	-N=N-Ph Cl-*p*	5	64	7	95
11 h	NH_2	-N=N-Ph F-*p*	5	63	8	92
11 i	NH_2	-N=N-Ph Br-*p*	5	68	5	91
11 j	NH_2	-N=N-Ph CH_3-*p*	5	63	7	93
11 k	NH_2	-N=N-Ph OCH_3-*p*	5	65	6	92

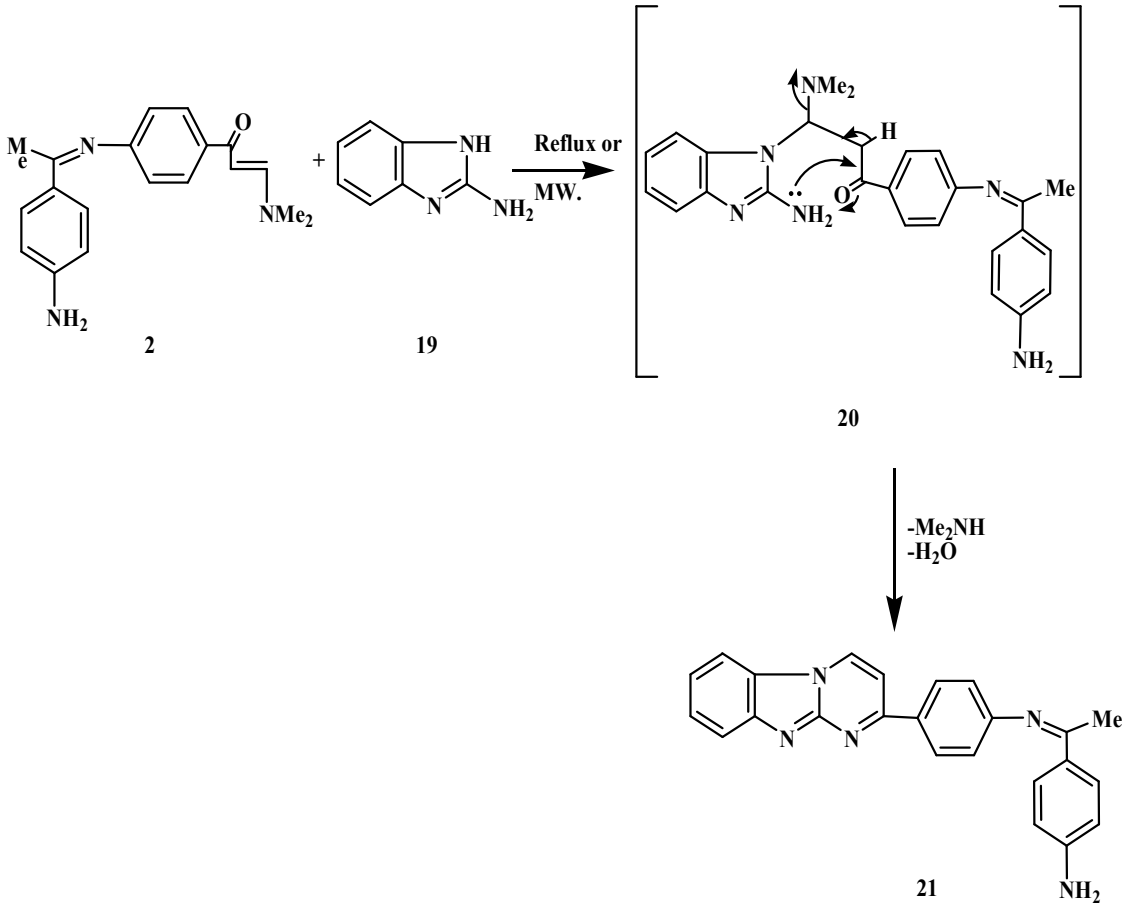
Enaminone **2** reacted with 3-amino-1,2,4-triazole (**15)** under microwave irradiation in presence of two drops of pyridine or in refluxing pyridine to afford 4-([1,2,4]triazolo[1,5-a]pyrimidin-7-yl)-N-(1(4aminophenyl) ethylidene)benzenamine (**17**) its structure was assigned based on its elemental analysis and spectral data For example, the mass spectrum revealed a molecular ion peak at *m/z* 328 its IR spectrum showed a two C=N bands at 1533, 1590 cm^{-1} and two asymmetric bands at 3262, 3297 cm^{-1} due to amino group Its ^1H NMR spectrum displayed a singlet signal at δ 2.09 due to(CH_3-C=N-), two doublet signals at δ 7.53, 8.85 due to pyrimidine protons and singlet signal at δ 8.66 due to triazole proton The multiplets in the region δ 7.64-8.39 is for aromatic protons. The NH_2 protons appeared as a D_2O exchangeable singlet at δ 10.30. A further evidence for the structure of compound **17** stems from an independent synthesis of it *via* reacting equimolar amounts of 1(4-(1-(4-aminophenyl)ethylideneamino)phenyl)ethanone (**1)** with 3-(*N,N*-dimethylaminomethylene)amino-1,2,4-triazole **(18)** in presence of two drops of pyridine under microwave irradiations or in refluxing pyridine afforded a product identical in all respects with structure **17** (Scheme 4).



Scheme 4

In contrast to the behavior of enaminone **2** towards aminopyrazole derivatives **9a-k,** and aminotriazole (**15)**, it reacted with 2-aminobenzimidazole (**19)** under microwave irradiation in presence of two drops of pyridine or in refluxing pyridine to afford only one isolable product (as examined by TLC). The reaction product was identified as 4-(pyrimido[1,2-a]benzimidazole-7-yl)-N-(1-(4aminophenyl) ethylidene) benzenamine (**21)** (Scheme 5). The spectral data of the isolated product **21** were in complete agreement with the assigned structure. For example, the mass spectrum revealed a molecular ion peak at *m/z* 378, its IR spectrum showed a two C=N bands at 1531, 1593 cm^{-1}, two asymmetric bands at 3266,3290 cm^{-1} due to amino group and revealed the absence of carbonyl absorption bands. Moreover, its ^1H NMR spectrum revealed singlet signal at δ 2.08 due to(CH_3-C=N-), two doublet signals at δ 7.10, 8.82 due to pyrimidine protons , and D_2O-exchangeable signals at δ 10.28 due to NH_2 protons, in addition to, a multiplet at δ 6.72-7.92 for aromatic protons.

The formation of compound **21** is assumed to take place *via* an initial *Michael-type* addition of the imino group (endocyclic nitrogen)[18,19] in compound **19** to the double bond in the enaminone **2** to give the acyclic non-isolable intermediate **20** which undergoes intramolecular cyclization and subsequent aromatization *via* the loss of dimethylamine and water molecules to afford the final isolable product **21** (Scheme 5). The discrepancy in the behavior of compounds **9a-k, 15** and 2-aminobenzimidazole **19** can be explained on the basis of steric factors**.**

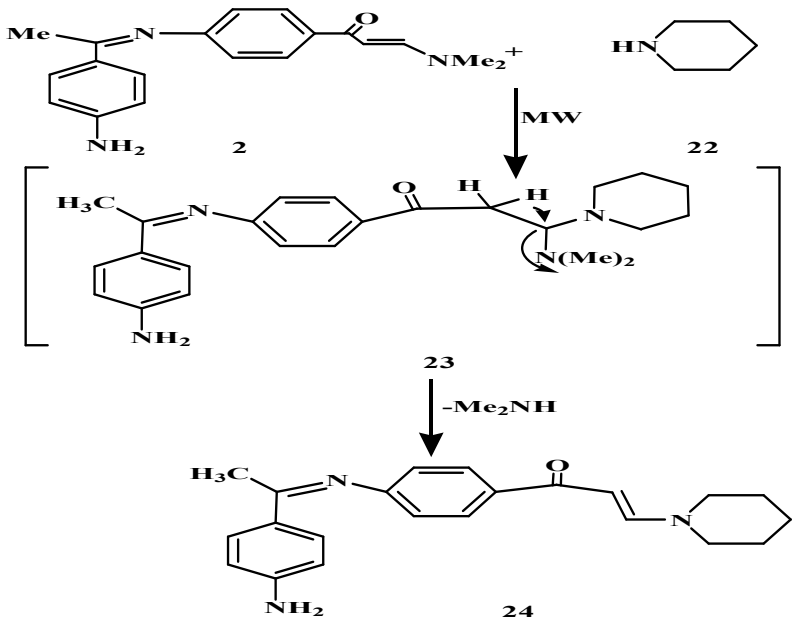


Scheme 5

The above results promoted us to extend our study to investigate the behavior of enaminone **2** towards piperdine (**22**) under the effect of microwave irradiation and compare the results with those obtained from reflux conditions.

Thus, when a mixture of enaminone **2** and piperdine (**22**) was refluxed for 14 hours in absolute ethanol or piperdine no reaction has occurred.

On the other hand, the reaction of enaminone **2** with piperdine (**22**) proceeded smoothly within 2 min. under microwave irradiation to afford only one isolable product (as examined by TLC). The reaction product was identified as E-1-(4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3-(piperidin-1-yl)prop-2-en-1-one **(24)** (Scheme 6). The spectral data of the isolated product **24** were in complete agreement with the assigned structure. For example, the mass spectrum revealed a molecular ion peak at *m/z* 348, its IR spectrum showed a C=N band at 1594 cm^{-1}, C=O band at 1671 and two asymmetric bands at 3255, 3293 cm^{-1} due to amino group. Moreover, its ^1H NMR spectrum are free of signals characteristic for the dimethylamine protons and revealed two multiplet signals at δ 1.57, 2.63 due to (CH_2 piperidine), singlet signal at δ 2.04 due to (CH_3-C=N-), , and D_2O-exchangeable signals at δ 10.28 due to NH_2 protons, in addition to, a multiplet at 7.55-8.12 due to 7.57-7.97 (m, 8H ArH's, 1H, -CO-CH=, 1H, =CH-N).



Scheme 6

Experimental

All organic solvents were purchased from commercial sources and used as received or dried using standard procedures unless other wise stated. All chemicals were purchased from Merck, Aldrich or Acros and used without further purification, thin layer chromatography (TLC) was performed on precoated merck 60GF254 silica gel plates with fluorescent indicator, and detection by means of UV light at 254 and 360 nm. 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 VXR-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in 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 were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Reactions carried out under microwave irradiation were performed in domestic microwave oven using 50 or 100% power

3-Aryl-5-amino-(1H)-Pyrazole (**9 a-e**) [20], 3,5-Diamino-4-arylazopyrazole [21] (**9 f-k**) were prepared according to literature procedures.

E-1-(-4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3-(dimethylamino)prop-2-ene-1-one (2)

Conventional method

A mixture of 1(4-(1-(4-aminophenyl)ethylideneamino) phenyl)ethanone (**1**) (30 mmol) and dimethylformamide-dimethylacetal *(DMF-DMA)* (50 mmol) was refluxed for 6 hours to give yellow precipitate. Recrystalization from acetone afforded E-1-(-4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3-(dimethylamino)prop-2-ene-1-one (**2**) in 70% yield

Green method

1(4-(1-(4-aminophenyl)ethylideneamino) phenyl)ethanone (**1**) (3 mmol) and dimethylformamide-dimethylacetal (DMF-DMA) (5 mmol) were mixed in a 10 ml glass vial , and subjected to a microwave irradiation for 2 minutes until completion of the reaction (monitored by TLC) the solid formed was purified by recrystallization from acetone to give product identical in all respects (mp, mixed mp, TLC, and comparative IR) with structure **2** in 93% yield.M.p.195-197°,IR (KBr): 1599 (C=N), 1690 (C=O) 3257, 3307 (NH_2) cm^{-1}.;^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H,CH_3-C=N), 2.90 (s, 3H, N-CH_3), 3.11 (s, 3H, N-CH_3), 5.77 (d, 1H, *J* = 12.6 Hz, -CO-CH=), 7.60-7.68 (m, 8H, Ar-H), 7.83 (d, *J* = 12.6 Hz, 1H, =CH-N). 10.09 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ: 25.51 ($\underline{C}H_3$C=N), 44.48(N$\underline{C}H_3$), 45.45 (N$\underline{C}H_3$), 91.44 (-CO-$\underline{C}$H=), 117.9, 129.8, 132.01, 135.2, 142, 144, 154.5 (aromatic), 169.50 (=$\underline{C}$H-N), 185.45($CH_3\underline{C}$=N), 196.99 ($\underline{C}$O); MS (*m/z*): 308 (M^+) Anal. for $C_{19}H_{21}N_3O$ (307.17). (Calcd: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.20 H, 6.90; N, 13.70.)

N(1-(4-aminophenyl)ethylidene)-4-(-2-aminopyrimidin-4-yl)benzenamine ***5***

Conventional method

A solution of guandine nitrate (**3**) (14.2 mmol) in absolute ethanol (15 ml) was added to a stirred solution of the enaminone **2** (11.3 mmol) in boiling absolute ethanol (10 ml), stirring was continued for 20 min. To this mixture, was added sodium ethoxide solution (22.6 mmol) in absolute ethanol (10 ml) and the reaction mixture was refluxed for 16 h, Then solution allow to cool to room temperature and the precipitate was removed by filtration followed by concentration of the filtrate under reduced pressure. The solid product that formed was collected by filtration, washed with water and dried. Recrystallization from ethanol/DMF (1:3) afforded the 2-aminopyrimidine derivative **5** in 70% yields**.**

Green method

An equimolar amount of enaminone **2** (5mmol), guanidine nitrate (5mmol) and sodium carbonate (0.5g) were mixed together in a tightly closed tube, and subjected to a microwave irradiation for 5 minutes until completion of the reaction (monitored by TLC) the solid formed was collected and purified by recrystallization from ethanol/DMF (1:3) to yield product identical in all respects (mp, mixed mp, TLC, and comparative IR) with **5** in 88% yields. M.p. over 300; IR (KBr): 1540 (C=N),1595 (C=N), 3257, 3307 (NH_2) 3350,3390 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) : 2.06 (s, 3H,CH_3-C=N),), 4.31 (s, 2H, NH_2 D_2O exchangeable), 6.88 (d, 1H, *J*=5.1 Hz pyrimidine-5-CH), 7.28-7.73 (m, 8H, ArH's), 8.40 (d, 1H, *J*=5.1 Hz pyrimidine-6-CH),10.09 (s, 2H, NH_2 D_2O exchangeable); MS (*m/z*): 304 (M^+); Anal. for $C_{18}H_{17}N_5$ (303.36).(Calcd: C, 71.27; H, 5.65; N, 23.09 Found: C, 71.30; H, 5.64; N, 23.07)

4-(1-(4-(1H-pyrazol-3-yl)phenylimino)ethyl)benzenamine **8**

Conventional method

Hydrazine hydrate (2 ml, 100%) was added to a stirred solution of the enaminone **2** (10 mmol) in absolute ethanol and the mixture was refluxed for 6 hours. The solid product was filtered off, washed with ethanol and recrystallized from ethanol/DMF (1:3) to afford 4-(1-(4-(1H-pyrazol-3-yl)phenylimino)ethyl)benzenamine **8** in 78% yield.

Green method

An equimolar amount of enaminone **2** (5mmol) and hydrazine hydrate were mixed together in a tightly closed tube, and subjected to a microwave irradiation for 2 min. until completion of the reaction (monitored by TLC) the solid formed was collected and purified by crystallization from ethanol/DMF (1:3) to afforded product identical in all respects (mp, mixed mp, TLC, and comparative IR) with **8** in 88% yield. M.p. = 166-168; IR (KBr): 1545(C=N), 1595 (C=N), 3187,3220 (NH_2) , 3328 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.03 (s, 3H,CH_3-C=N), , 6.62 (d, 1H, *J*=1.8 Hz pyrazole-4-CH), 7.6-7.71 (m, 8H, ArH's), 7.70 (d, 1H, *J*=1.8 Hz pyrazole-5-CH),9.97 (s, 2H, NH_2 D_2O exchangeable), 12.81 (s, 1H, NH, D_2O-exchangable); MS (*m/z*): 277 (M^+); Anal. for $C_{18}H_{19}N_5$ (276.34). (Calcd: C, 73.89; H, 5.84; N, 20.27 Found: C, 73.97; H, 5.78; N, 20.25.)

Reaction of E-1-(4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3-(dimethylamino)prop-2-ene-1-one (**2**) with 5-amino-3-aryl-4-substituted pyrazole (**9a-k**)

Conventional methods

Method A

To a mixture of **(**2E)-1-(4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3-(dimethylamino)prop-2-ene-1-one (**2)** (10 mmol) and the appropriate aminopyrazole derivative (10 mmol), in absolute ethanol (25 ml), few drops of piperidine was added and the reaction mixture was refluxed for 5h. The solid product was filtered off, washed with ethanol and recrystallized from ethanol/DMF to afford the pyrazolo[1,5-*a*]pyrimidine derivatives (**11a-k)** in 62-68% yield.

Method B

To a mixture 4-(1-(4-aminophenyl)ethylideneamino)phenyl)ethanone (**1)** (10 mmol) and an equivalent molar ratio of 5-*N*-(*N,N*-dimethylaminomethylene)amino-3,4-disubstituted-1H-pyrazol **(14)**, in absolute ethanol (25 ml), few drops of piperidine was added and the reaction mixture was refluxed for 7hrs. The solid product was filtered off, washed with ethanol and recrystallized from ethanol/DMF afforded product identical in all respects (mp, mixed mp, TLC, IR and mass spectra with **11**)

Green methods

Method A

An equimolar amount of enaminone **2** (5mmol) and the appropriate aminopyrazole derivatives were mixed together in a tightly closed tube in the presence of 2 drops of piperidine as a catalyst, and subjected to a microwave irradiation for the appropriate time in 1 min intervals (Table 2) until completion of the reaction (monitored by TLC) the solid formed was collected and purified by crystallization to afford product identical in all respects (mp, mixed mp, TLC, and comparative IR) with **11** in90-95% yields.

Method B:

A mixture of 1(4-(1-(4-aminophenyl)ethylideneamino)phenyl)ethanone (**1**) (10 mmol) and an equivalent molar ratio of 5-*N*-(*N,N*-dimethylaminomethylene)amino-3,4-disubstituted-1H-pyrazol **(14)** in the presence of 2 drops of pyridine, was subjected to a microwave irradiation for the appropriate time in 1 min. intervals until completion of the reaction (monitored by TLC). The precipitated solid product was collected and purified by Recrystalization from ethanol/DMF (1:2) afforded product identical in all respects (mp, mixed mp, TLC, IR and mass spectra) with **11a-k**. The synthesized compounds with their physical data are listed below

N-(1-(4-aminophenyl)ethylidene)-4-(2-phenylpyrazolo[1,5-a]pyrimidin -7-yl)benzenamine (**11a**)

M.p. 88-90 °C; IR (KBr): 1550(C=N), 1598 (C=N), 3220, 3300 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.07 (s, 3H,CH_3-C=N) , 7.22(d, 1H, *J*= 4.5 Hz pyrimidine-6-CH), 7.28 (s, 1H, pyrazole-3-CH), 7.33-8.28 (m, 13H, ArH's), 8.55 (d, 1H, *J*= 4.5 Hz pyrimidine-5-CH), 10.27 (s, 2H, NH_2 D_2O exchangeable); MS (*m/z*):405 (M^+) Anal. for $C_{26}H_{21}N_5$ (403.48). (Calcd: C, 77.40; H, 5.25; N, 17.36 Found: C, 77.45; H, 5.19; N, 17.37).

N-(1-(4-aminophenyl)ethylidene)-4-(2-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-yl)benzenamine (**11b**)

M.p.118-119 °C ; IR (KBr): 1530 (C=N), 1599 (C=N), 3220, 3290 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.11 (s, 3H,CH_3-C=N) , 7.23(d, 1H, *J*= 3.6 Hz pyrimidine-6-CH), 7.31 (s, 1H, pyrazole-3-CH), 7.53-8.26 (m, 12H, ArH's), 8.55 (d, 1H, *J*= 3.6 Hz pyrimidine-5-CH), 10.26 (s, 2H, NH_2 D_2O exchangeable); MS (*m/z*):328 (M^+). Anal. for $C_{26}H_{20}ClN_5$ (437.92).(Calcd: C, 71.31; H, 4.60; Cl, 8.10; N, 15.99. Found: C, 71.35; H, 4.51; Cl, 8.12; N, 16.02.)

N-(1-(4-aminophenyl)ethylidene)-4-(2-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-7-yl)benzenamine (**11c**)

M.p. 165-166 °C; IR (KBr): 1540 (C=N), 1592 (C=N), 3258, 3299 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.11 (s, 3H,CH_3-C=N), 3.78 (OCH_3), 7.03(d, 1H, *J*= 4.5 Hz pyrimidine-6-CH), 7.18 (s, 1H, pyrazole-3-CH), 6.90-8.27 (m, 12H, ArH's), 8.50 (d, 1H, *J*= 4.5 Hz pyrimidine-5-CH), 10.39 (s, 2H, NH_2 D_2O exchangeable); MS (*m/z*):435 (M^+) Anal. for $C_{27}H_{23}N_5O$. (Calcd: C, 74.81; H, 5.35; N, 16.16 Found: C, 74.83; H, 5.38; N, 16.11)

N-(1-(4-aminophenyl)ethylidene)-4-(2-methylpyrazolo[1,5-a]pyrimidin-7-yl)benzenamin(**11d**) M.p.78-80 °C; IR (KBr): 1540(C=N), 1602 (C=N), 3261, 3350 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ= 2.10 (s, 3H,CH_3-C=N), 2.50 (s, 3H,CH_3 pyrazole), 6.57 (s, 1H, pyrazole-3-CH), 7.10(d, 1H, J= 4.5 Hz pyrimidine-6-CH), , 7.76-8.15 (m, 8H, ArH's), 8.47 (d, 1H, J= 4.5 Hz pyrimidine-5-CH), 10.24 (s, 2H, NH_2 D_2O exchangeable); MS (m/z):340 (M^+) ; Anal. for $C_{21}H_{19}N_5$, (Calcd: C, 73.88; H, 5.61; N, 20.51 Found: C, 73.95; H, 5.58; N, 20.47)

N-(1-(4-aminophenyl)ethylidene)-4-(2-methyl-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)benzenamine (**11e**)

M.p.285-287 °C; IR (KBr): 1520 (C=N), 1596 (C=N) and 3350, 3400 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ= 2.08 (s, 3H,CH_3-C=N), 2.54 (s, 3H,CH_3 pyrazole), 7.15(d, 1H, J= 4.6 Hz pyrimidine-6-CH), , 7.44-8.26 (m, 13H, ArH's), 8.52 (d, 1H, J= 4.6 Hz pyrimidine-5-CH), 10.34 (s, 2H, NH_2 D_2O exchangeable); MS (m/z): 418 (M^+); Anal. for $C_{27}H_{23}N_5$, (Calcd: C, 77.67; H, 5.55.; N, 16.77, Found: C, 77.71; H, 5.50; N, 16.78.)

N-(1-(4-aminophenyl)ethylidene)-4-((2-Amino-3-phenylazo)pyrazolo[1,5-a]pyrimidin-7-yl)benzenamine(**11f**) M.p. over 300; IR (KBr) ν_{max}/cm^{-1}: 1520 (C=N), 1610 (C=N), 3200,3260 (NH_2), 3392,3410 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.11 (s, 3H,CH_3-C=N), 4.32 (br' s, 2H, NH_2, exchangeable D_2O), 7.21(d, 1H, J= 4.8 Hz pyrimidine-6-CH), 7.27-8.16 (m, 13H, ArH's), 8.53 (d, 1H, J= 4.8 Hz pyrimidine-5-CH), 10.26 (s, 2H, NH_2 D_2O exchangeable); MS (m/z): 447 (M^+); Analysis for$C_{26}H_{22}N_8$, (Calcd: C, 69.94; H, 4.97; N, 25.10 Found: C, 69.99; H, 4.95; N, 25.07)

N-(1-(4-aminophenyl)ethylidene)-4-((2-Amino-3-(4-chlorophenylazo))pyrazolo[1,5-a]pyrimidin-7-yl)benzenamine(**11g**)

M.p.122-124 °C; IR (KBr): 1535 (C=N), 1590 (C=N), 3200,3296 (NH_2), 3380,3420 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ= 2.07 (s, 3H,CH_3-C=N), 4.25 (br' s, 2H, NH_2, exchangeable D_2O), 7.30(d, 1H, J= 4.8 Hz pyrimidine-6-CH), , 7.27-8.16 (m, 12H, ArH's), 8.45 (d, 1H, J= 4.8 Hz pyrimidine-5-CH), 10.24 (s, 2H, NH_2 D_2O exchangeable); MS (m/z): 482 (M^+); Analysis for$C_{26}H_{21}ClN_8$.(Calcd: C, 64.93; H, 4.40; Cl,7.37; N, 23.30; Found: C, 64.96; H, 4.35; Cl, 7.43; N, 23.26).

N-(1-(4-aminophenyl)ethylidene)-4-((2-Amino-3-(4-flourophenylazo))pyrazolo[1,5-a]pyrimidin-7-yl)benzenamine(**11h**) M.p.120-122 °C; IR (KBr): 1541 (C=N), 1595 (C=N), 3190,3280 (NH_2), 3387,3425 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ= 2.07 (s, 3H,CH_3-C=N), 4.24 (br' s, 2H, NH_2, exchangeable D_2O), 7.19(d, 1H, J= 4.8 Hz pyrimidine-6-CH), , 7.20-8.14 (m, 12H, ArH's), 8.53 (d, 1H, J= 4.8 Hz pyrimidine-5-CH), 10.27 (s, 2H, NH_2 D_2O exchangeable); MS (m/z): 465 (M^+); Anal. for$C_{26}H_{21}FN_8$. (Calcd: C, 67.23; H, 4.56; F, 4.09; N, 24.12; Found: C, 67.32; H, 4.51; F, 4.14; N, 24.03).

N-(1-(4-aminophenyl)ethylidene)-4-((2-Amino-3-(4-bromophenylazo))pyrazolo[1,5-a]pyrimidin-7-yl)benzenamine(**11i**) M.p. over 300 °C; IR (KBr) ν_{max}/: 1520 (C=N), 1622 (C=N), 3180,3260 (NH_2), 3380,3414 (NH_2)cm^{-1}; ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H,CH_3-C=N), 4.20 (br' s, 2H, NH_2, exchangeable D_2O), 7.26(d, 1H, J= 4.8 Hz pyrimidine-6-CH), 7.65-8.14 (m, 12H, ArH's), 8.56 (d, 1H, J= 4.8 Hz pyrimidine-5-CH), 10.26 (s, 2H, NH_2 D_2O exchangeable); MS (m/z): 525 (M^+); Analysis for$C_{26}H_{21}BrN_8$, (Calcd: C, 59.44; H, 4.03; Br,15.21; N, 21.33; Found: C, 59.50; H, 4.00; Br, 15.25; N, 21.26).

N-(1-(4-aminophenyl)ethylidene)-4-((2-Amino-3-(4-methyl phenylazo))pyrazolo[1,5-a]pyrimidin-7-yl)benzenamine (**11j**) M.p. 280-282 °C; IR (KBr) ν_{max}/: 1545 (C=N), 1612 (C=N), 3195,3265 (NH_2), 3390,3423 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ= 2.10 (s, 3H,CH_3-C=N), 2.35(s, 3H, CH_3) 4.59 (br' s, 2H, NH_2, exchangeable D_2O), 7.17(d, 1H, J= 4.8 Hz pyrimidine-6-CH), , 7.23-8.12 (m, 12H, ArH's), 8.54 (d, 1H, J= 4.8 Hz pyrimidine-5-CH), 10.25 (s, 2H, NH_2 D_2O exchangeable); MS (m/z): 459 (M^+); Analysis for$C_{27}H_{24}N_8$. (Calcd: C, 70.42; H, 5.25; N, 24.33; Found: C, 70.48; H, 5.23; N, 24.29).

N-(1-(4-aminophenyl)ethylidene)-4-((2-Amino-3-(4-methylphenylazo)) pyrazolo[1,5-a]pyrimidin-7-yl)benzenamine (**11k**) M.p. 225-226 °C; IR (KBr): 1600 (C=N), 1629 (C=N), 3187, 3266 (NH_2), 3401,3420 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): = 2.11 (s, 3H,CH_3-C=N), 3.83(s, 3H, OCH_3) 4.53 (br' s, 2H, NH_2, exchangeable D_2O), 7.20 (d, 1H, J= 4.5 Hz pyrimidine-6-CH), , 7.04-8.16 (m, 12H, ArH's), 8.53 (d, 1H, J= 4.5 Hz pyrimidine-5-CH), 10.18 (s, 2H, NH_2 D_2O exchangeable); MS (m/z): 477 (M^+); Analysis for$C_{27}H_{24}N_8O$, (Calcd: C, 68.05; H, 5.08; N, 23.51; Found: C, 68.12; H, 5.05; N, 23.47).

Reaction of E-1-(4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3-(dimethylamino)prop-2-ene-1-one (**2**) with 3-amino-1,2,4-triazole (**15**) and 2-amino-benzimidazole (**19**)

Conventional method

Method A:

a mixture of (2E)-1-(4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3-(dimethylamino)prop-2-ene-1-one (**2**) (10 mmol) and the appropriate heterocyclic amine (3-amino-l,2,4-triazole (**15**) **or** 2-aminobenzimidazole (**19**)) 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 ethanol then filtered, washed with water, dried and finally recrystallized from appropriate solvent to afford the corresponding triazolo[1,5-a]pyrimidine or pyrimido[1,2-a]benzimidazole derivatives **17** or **21**, respectively.

Method B:

A mixture of (4-(1-(4-aminophenyl)ethylideneamino)phenyl)ethanone (**1**) (10 mmol) and an equivalent molar ratio of 3-(N,N-dimethylaminomethylene)amino-1,2,4-triazole (**18**) in pyridine (25 ml) was refluxed for 8 h, then left to cool. The solvent was evaporated in vacuo and the residual solid was collected and recrystallized from ethanol to afford product identical in all respects (mp, mixed mp, TLC, IR and mass spectra) with **17**.

Green methods

Method A:

To a mixture E-1-(4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3-(dimethylamino)prop-2-ene-1-one (**2**) (10 mmol) and the appropriate heterocyclic amine (3-amino-l,2,4-triazole (**15**) or 2-aminobenzimidazole **(19)**) (10mmol) was added 2 drops of pyridine in a tightly closed tube, and subjected to a microwave irradiation for the appropriate time in 1 min. intervals (table 1) until completion of the reaction (monitored by TLC) the Solid formed was purified by crystallization from appropriate solvent to afford the corresponding triazolo[1,5-a]pyrimidine (**17**) or pyrimido[1,2-a]benzimidazole (**21**) derivatives

Table 2: synthesis of triazolo[1,5-a]pyrimidine (17) and pyrimido[1,2-*a*]benzimidazole (21) under microwave irradiation and conventional method

Product	Reflux		Microwave	
	Time (h)	Yield (%)	Time (min.)	Yield (%)
17	12	68	3	94
21	12	65	7	90

Method B

A mixture of (4-(1-(4-aminophenyl)ethylideneamino)phenyl)ethanone 2 (10 mmol) and an equivalent molar ratio of 3-(N,N-dimethylaminomethylene)amino-1,2,4-triazole **(18)**

in the presence of 2 drops pyridine, was subjected to a microwave irradiation in 1 min intervals until completion of the reaction (monitored by TLC) after 5 min. The precipitated solid product was collected by filtration, recrystalized from ethanol to afford product identical in all respects (mp, mixed mp, TLC, IR and mass spectra with **17**).

4-([1,2,4]triazolo[1,5-a]pyrimidin-7-yl)-N-(1-(4aminophenyl) ethylidene)benzenamine (**17**)
M.p. 131-132 °C; IR (KBr): 1533 (C=N), 1590 (C=N), 3262,3297 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 09 (s, 3H,CH_3-C=N), 7.53(d, 1H, J= 4.5 Hz pyrimidine-6-CH), 7.64-8.39 (m, 8H, ArH's), 8.66(s, 1H, CH triazole), 8.85 (d, 1H, J= 4.5 Hz pyrimidine-5-CH), 10.30 (s, 2H, NH_2 D_2O exchangeable); MS (m/z): 328 (M^+); Anal. for $C_{19}H_{16}N_6$. (Calcd: C, 69.50; H, 4.91; N, 25.59, Found: C, 69.57; H, 4.87; N, 25.56).

4-(pyrimido[1,2-a]benzimidazole-7-yl)-N-(1-(4aminophenyl) ethylidene)benzenamine (**21)**
M.p.129-130 °C ; IR (KBr): 1531 (C=N), 1593 (C=N), 3266,3290 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.08 (s, 3H,CH_3-C=N), 7.10(d, 1H, J= 4.2 Hz pyrimidine-6-CH), 6.72-7.92 (m, 12H, ArH's), 8.82 (d, 1H, J= 4.2 Hz pyrimidine-5-CH), 10.28 (s, 2H, NH_2 D_2O exchangeable); MS (m/z): 378 (M^+); Analysis for$C_{24}H_{19}N_5$. (Calcd: C, 76.37; H, 5.07; N, 18.55; Found: C, 76.43; H, 5.04; N, 18.52.)

E-1-(4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3-(piperidin-1-yl)prop-2-en-1-one (**23**)
Conventional method
A mixture of E-1-(4-(1-(4-aminophenyl)ethylideneamino)phenyl)-3-(dimethylamino)prop-2-ene-1-one (**2**) (5 mmol) and piperidine (**22**) (3 ml) in ethanol (30 ml) was refluxed for 20 h. No reaction has been occurred. The mixture was refluxed in absence of ethanol for 14 hours. No reaction has been observed.
Green method
An equimolar amount of enaminone **2** (5mmol) and piperidine (**22**) were mixed together in a tightly closed tube and subjected to a microwave irradiation for 2min. The progress of the reaction was monitored by TLC. After completion of the reaction the solid formed was purified by crystallization from ethanol to afford structure **23.** M.p. =over 300; IR (KBr): 1594 (C=N), 1671 (C=O), 3255,3293 (NH_2) cm^{-1}; 1H NMR (DMSO-d6)δ: 1.57 (m, 6H, CH_2 piperidine), 2.04 (s, 3H,CH_3-C=N), 2.63 (m, 4H, CH_2 piperidine), 7.57-7.97 (m, 8H ArH's, 1H, -CO-CH=, 1H, =CH-N), 10.28 (s, 2H, NH_2 D_2O exchangeable); MS (m/z): 348 (M^+); Anal. for $C_{22}H_{25}N_3O$ (347.45), (Calcd: C, 76.05; H, 7.25; N, 12.09; Found: C, 76.12; H, 7.22; N, 12.06).

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