Microwave-Assisted Synthesis of Novel Pyrazole, Pyrimidine and Pyrazolo[1,5-a]pyrimidines Containing Aryl Sulfone Moiety

Ahmed A. El-Kateb[1], Naglaa M. Abd El-Rahman[1,2,*], Tamer S. Saleh[1,3], Ibrahim F. Zeid[4], Mohamed F. Mady[1]

[1]Green Chemistry Department, National Research Centre, Dokki, Cairo, 12622, Egypt
[2]Chemistry department, Faculty of Science, Jazan University, Jazan, Saudi Arabia
[3]Chemistry Department, Faculty of Science, King AbdulAziz University, Jeddah, Saudi Arabia
[4]Chemistry Department, Faculty of Science, El-Menoufia University, Shebin El-Koam, El-Menoufia, Egypt
naglaa_r@yahoo.com

Abstract: A facile, rapid and efficient microwave-assisted procedure for the synthesis of novel pyrazole, pyrimidine, and pyrazolo[1,5-a]pyrimidines linked to sulfonyl dibenzene moiety *via* the reaction of *E*-3-(*N*,*N*-dimethylamino)-1-(4-(phenylsulfonyl)phenyl)prop-2-en-1-one **3** with the appropriate amines described here. In general, microwave procedure as an eco-friendly energy source offers advantages such as a shorter reaction time, simple workup, reaction selectivity and improves an overall yield compared with conventional methods. The structures of all the compounds were confirmed by analytical and spectral data.
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1. Introduction:

Pyrazolopyrimidines are found to possess a wide important pharmacophore and adjective structure in medicinal chemistry due to their biological importance. Functionalized pyrazolopyrimidines are known to exhibit several pharmacological activities such as CNS depressant **[1]**, antihypertensive **[2],** adenosine receptors **[3],** tuberculostatic **[4],** antibacterial and antifungal **[5].** Some of the pyrazolopyrimidine derivatives are known to inhibit enzymes such as xanthine oxidase **[6,7].**

The pyrazolo[1,5-a]pyrimidines frame work, are attractive compounds for drug discovery since many of them have been shown to exhibit excellent biological activities **[8].** In addition, the pyrimidines and pyrazoles have received much attention over their years because of their interesting pharmacological properties **[9,10]**.

Aryl sulfone structure is featured in a variety of pharmacological and biological active compounds. These compounds include antifungal, antibacterial, or antitumor agents **[11,12],** and inhibitors for several enzymes **[13,14**]. In addition, the Sulfone moiety is usually incorporated as an active part in many analgesic anti-inflammatory molecules available as drugs in market such as celecoxib **[15,16],** valdecoxib [**17],** rofecoxib **[18],** parecoxib **[19],** etoricoxib **[20**], tenoxicam **[21],** piroxicam **[22],** meloxicam **[23],** lornoxicam **[24],** ampiroxicam **[25]** and nimesulide **[26]**.

The development of simple and eco-friendly synthetic procedures constitutes an important goal in organic synthesis. Microwave assisted organic synthesis (MAOS) is a fast growing area of research, due to the generally short reaction times, high purities and yields of the resulting products when compared to conventional methods **[27].** In addition, Solvent-free reactions under microwave irradiation are the subject of constant development because of its ease of set-up, mild conditions, and increased yields of products, cost efficiency and environment friendliness compared to their solution counterparts **[28].**

In continuation of our recent work aiming at the synthesis of a variety of heterocyclic systems using green chemistry tools **[27,29-31**], we focus in this article on a practical, rapid, and efficient microwave (MW) promoted synthesis of novel pyrazole, pyrimidine and pyrazolo[1,5-a]pyrimidines containing the aryl sulfone moiety compared with conventional methods.

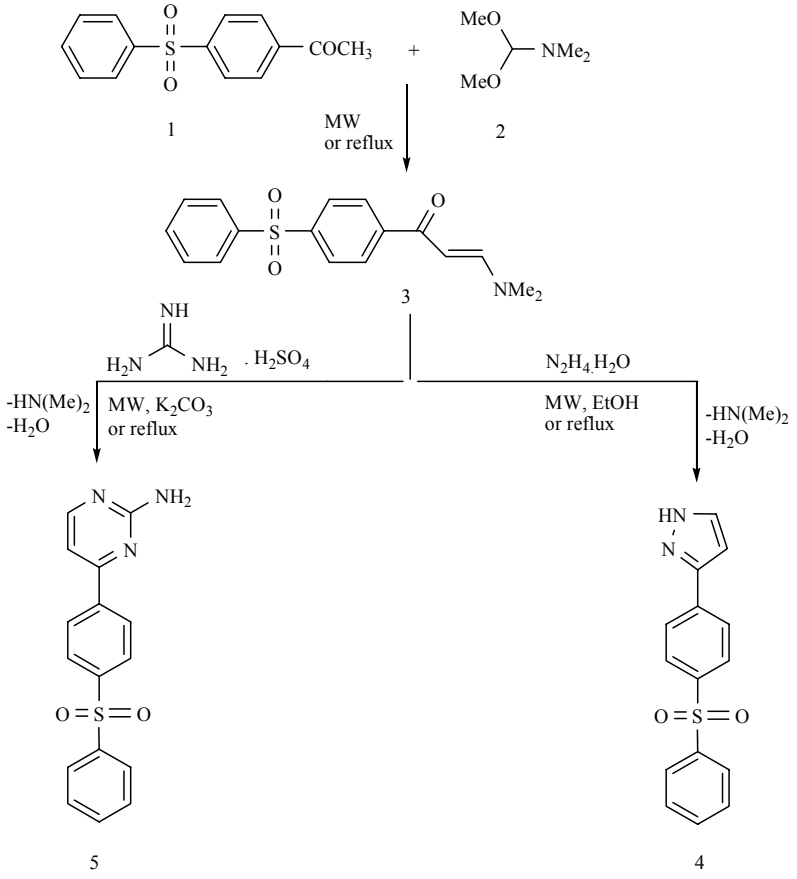
2. Results and Discussion

Firstly, a simple, efficient and solvent-free reaction for condensation of 1-acetyl-4-(phenylsulfonyl)benzene **1** with dimethylformamide-dimethylacetal (DMFDMA) **2** under microwave irradiation for 20 min. providing the corresponding *E*-3-(dimethylamino)-1-(4-(phenylsulfonyl)phenyl) prop-2-en-1-one **3** in 90 % yield compared with conventional heating reaction in dry toluene for 12hr in 70% yield (Scheme 1). The structure of the enaminone **3** was established on the basis of their elemental analysis and spectral data. The ^{1}H NMR spectrum of **3** displayed a singlet signals at δ 2.91

and 3.14 due to *N*,*N*-dimethyl protons, two doublets at δ 5.78 and 7.74 (*J*=12.3 Hz) due to olefinic protons, in addition to an aromatic multiplets in the region δ 7.63-8.06, the value of the coupling constant (*J* = 12.3 Hz) for the ethylenic protons indicates that the enaminone **3** exists exclusively in the *E*-configuration **[32].**

Enaminones are valuable intermediates in synthetic organic chemistry **[33,34]**. Thus, the enaminone **3** underwent cyclocondensation on treatment with hydrazine hydrate under microwave irradiation in presence of ethanol or refluxing in ethanol to afford, in each case, 3-(4-(phenylsulfonyl)phenyl)-1H-pyrazole **4** (Scheme 1). In case of conventional method the product was obtained in good yield up to 71% within 5h. While under microwave irradiation the obtained yield was excellent up to 89% in 30 min. The structure of 3-(4-(phenylsulfonyl)phenyl)-1H-pyrazole **4** was established on the basis of its elemental analysis and spectral data. For example, its IR spectrum showed NH absorption band at 3059 cm^{-1}. the ^1H NMR spectrum of the same compound revealed two doublet signals at δ 6.83 and 7.60 with *J* values = 1.5 Hz due to pyrazole protons and D_2O-exchangeable signal at δ 13.11 due to NH proton, in addition to an aromatic multiplet at δ 7.59-8.05.

Additionally, treatment of enaminone **3** with guanidine sulfate in presence of potassium carbonate as an efficient catalyst under microwave irradiation, afforded 2-amino-4-(4-(phenylsulfonyl)phenyl) pyrimidine **5** in 95% yield within 1 h. Similarly, repeating the same reaction under the conventional heating conditions by refluxing in ethanol in presence of potassium carbonate, the yield into 85% and increase the time up to 7 h (scheme 1).

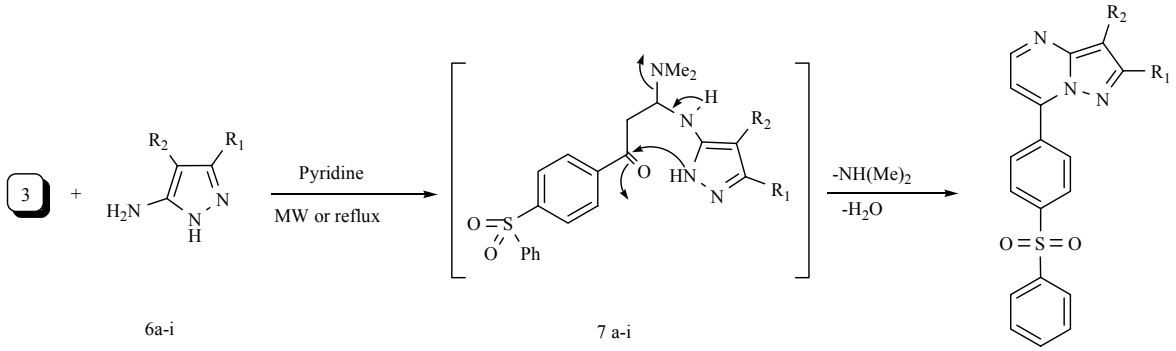


Scheme 1. Synthesis of 3-(4-(phenylsulfonyl)phenyl)-1H-pyrazole **4** and 2-amino-4-(4 (phenylsulfonyl)phenyl)pyrimidine **5** under microwave irradiation or conventional conditions.

On the other hand, the behavior of enaminone towards some aminopyrazole derivatives as potential precursors for interesting biologically active pyrazolo[1,5-a]pyrimidine derivatives was investigated **[35]**. Thus, when enaminone **3** was treated with aminopyrazoles **6a-i** under microwave irradiation in presence of a catalytic amount of pyridine or conventional heating under reflux in

pyridine, afforded, in each case, pyrazolo[1,5-a]pyrimidine **8a-i** in high yield as shown in table 1 (Scheme 2).

A plausible mechanism for the formation of compounds 8a-i is therefore assumed to take place *via* an initial Michael addition of the exocyclic amino group in the aminopyrazoles **6a-i** to the α,β-unsaturated moiety in the enaminone **3** to give the acyclic non-isolable intermediates **7a-i** followed by cyclization and aromatization of the latter intermediates, under the reaction condition *via* the loss of a water and dimethyamine molecules to afford the pyrazolo[1,5-a]pyrimidines **8a-i** (Scheme 2). The products **8a-i** were obtained in good yields up to 70% in case of conventional method. While under microwave irradiation the yields obtained were excellent up to 93% as illustrated in table 1. The structures of compounds **8a-i** were established on the basis of their elemental analyses and spectral data. For example the IR spectrum of compound **8f** shows two bands at 3423, 2928 cm^{-1} due to amino group. The ^1H NMR spectrum of the same compound exhibited singlet signal at δ 2.36 (CH_3), also, one singlet signal (D_2O-exchangeable) assigned to NH_2 protons at δ= 7.12, and two doublet signals at δ= 7.24, 8.62 (J = 4.5 Hz) due to pyrimidine protons (CH-6 and CH-5 respectively), in addition, aromatic protons as a multiplet at δ 7.23-8.25 ppm. The mass spectrum of compound **8f** reveals a molecular ion peak at m/z 468 (*cf*. experimental part).



6-8	R_1	R_2
a	C_6H_5	H
b	C_6H_4Cl-*p*	H
c	$C_6H_4OCH_3$-*p*	H
d	Me	Ph
e	NH_2	-N=N-C_6H_5
f	NH_2	-N=N-$C_6H_4CH_3$-*p*
g	NH_2	-N=N-$C_6H_4OCH_3$-*p*
h	NH_2	-N=N-C_6H_4F-*p*
i	NH_2	-N=N-C_6H_4Br-*p*

Scheme 2. Synthesis of pyrazolo[1,5-a]pyrimidine derivatives **8a-i** under microwave irradiation and conventional conditions.

Table 1. Synthesis of pyrazolo[1,5-a]pyrimidine derivatives **8a-i** under microwave irradiation and conventional conditions

Product	**R_1**	**R_2**	**Microwave**		**Conventional**	
			Time (min)	Yield (%)	Time (h)	Yield (%)
8a	C_6H_5	H	30	89	5	70
8b	C_6H_4Cl-*p*	H	15	92	5	80
8c	$C_6H_4OCH_3$-*p*	H	20	90	5	75
8d	Me	C_6H_6	30	90	5	72
8e	NH_2	-N=N-C_6H_5	45	91	5	77
8f	NH_2	-N=N-$C_6H_4CH_3$-*p*	60	89	5	70
8g	NH_2	-N=N-$C_6H_4OCH_3$-*p*	45	90	5	75
8h	NH_2	-N=N-C_6H_4F-*p*	30	93	5	83
8i	NH_2	-N=N-C_6H_4Br-*p*	45	92	5	80

Table 1 indicated that there was a remarkable microwave effect on the reaction of enaminone **3** with some aminopyrazole derivatives, the target products **8a-i** were afforded in excellent yields greater than 92% within dramatically shortened time (15-60 min). Evidently, the Microwave effect might be the significant factor to the highly efficient synthesis of pyrazolo[1,5-a]pyrimidine derivatives.

3. Experimental Section

The chemicals used in this work were obtained from Fluka and Merck and were used without purification. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Microwave experiments were carried out using a CEM Discover Labmate Microwave apparatus (300 W with Chem. Driver software). Reactions were monitored by thin layer chromatography using Fluka GF254 silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm. IR spectra were recorded on KBr disks on a Perkin Elmer 2000 FTIR spectrometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer at 300.13 and 75.47MHz. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterated chloroform ($CDCl_3$) or dimethylsulphoxide (DMSO-d6) using TMS as the internal standard. ^{13}C chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Micro analytical Center of Cairo University, Giza, Egypt.

1-acetyl-4-(phenylsulfonyl)benzene**1[36],** 5-amino-3-methyl-1H-pyrazole **6a[37**], 5-amino-3-methyl-4-phenyl-1H-pyrazole **6d[38],**and 4-(arylhydrazono)-3,5-diamino-1H-pyrazole **6e–i[37**], were prepared according to literature procedures.

Synthesis of *E*-3-(dimethylamino)-1-(4-(phenylsulfonyl)phenyl)prop-2-en-1-one 3

Method A: under microwave irradiation

A mixture of 1-acetyl-4-(phenylsulfonyl)benzene **1** (26.0 g, 100 mmole) and DMFDMA **2** (13.4 g, 100 mmol) was irradiated by focused microwaves (at 180 °C, 300 W) for 20 min. After the irradiation, the reaction was cooled until the temperature had fallen below 50 °C. The solid product, so formed, was collected by filtration and crystallized from ethanol to give compound **3** in 90% yields.

Method B: under conventional conditions

To a solution of 1-acetyl-4-(phenylsulfonyl)benzene **1** (26.0 g, 100 mmole) in dry toluene (150 ml) was added dimethylformamide-dimethylacetal (DMF-DMA) **2** (13.4 g, 100 mmol) and the mixture was refluxed for 12 h. The solvent was distilled off at reduced pressure and the residual reddish brown viscous liquid was taken in petroleum ether (bp. 60-80 °C) (20 ml) then the resulting reddish yellow crystal was collected by filtration, washed thoroughly with ether, dried and finally crystallized from ethanol to afford *E*-3-(dimethylamino)-1-(4-(phenylsulfonyl)phenyl) prop-2-en-1-one **3** in 70% yield.

E-3-(dimethylamino)-1-(4-(phenylsulfonyl)phenyl) prop-2-en-1-one **(3).**

m.p.; 125-127 °C; IR (KBr) νmax/cm^{-1}:1643 (C=O), 1300, 1155 (SO_2); ^{1}H NMR (DMSO-d6): δ 2.91 (s, 3H, NCH_3), 3.14 (s, 3H, NCH_3), 5.78 (d, 1H, J = 12.3 Hz, -CO-CH=), 7.62-8.06 (m, 9H, Ar-H), 7.74 (d, 1H, J = 12.3 Hz, =CH-N); ^{13}C NMR (DMSO-d6): δ 44.63, 91.06, 120.55, 127.51, 128.23, 129.34, 133.80, 140.83, 142.37, 144.68, 155.01, 184.01; MS (*m/z*): 315 (M^+). (Found: C, 64.74; H, 5.43; N, 4.44; S, 10.17 $C_{17}H_{17}NO_3S$ requires C, 64.72; H, 5.45; N, 4.46; S, 10.16).

Synthesis of 3-(4-(phenylsulfonyl)phenyl)-1H-pyrazole 4

Method A: under microwave irradiation

To an equimolar amounts of *E*-3-(dimethylamino)-1-(4-(phenylsulfonyl)phenyl)prop-2-en-1-one **3**, hydrazine hydrate (2 mmol, 100%), ethanol (10 ml). The mixture was then subjected to microwave irradiation (at 80 °C, 300 W) for 30 min. until consumption of reactants as determined by TLC. After cooling to room temperature, the precipitated product was recrystallized from ethanol, to give the corresponding 3-(4-(phenylsulfonyl)phenyl)-1H-pyrazole **4** in 89% yields.

Method B: under conventional Conditions

To a mixture of *E*-3-(dimethylamino)-1-(4-(phenylsulfonyl)phenyl)prop-2-en-1-one **3** (0.315 g, 1mmol) and hydrazine hydrate (2 mmol, 100%), in ethanol (25 ml), the reaction mixture was refluxed for 5h. The solid product was filtered off, washed with ethanol and recrystallized from ethanol to afford the pure product **4** in 71% yields. The physical and spectral data of the synthesized compound **4** is listed below.

3-(4-(phenylsulfonyl)phenyl)-1H-pyrazole **(4).**

m.p.; 238-240°C; IR (KBr) υmax /cm^{-1}: 3059 (NH), 1312, 1154 (SO_2); ^{1}H NMR (DMSO-d6): 6.83 (d, 1H, J = 1.5 Hz pyrazole -4-CH), 7.59-8.05 (m, 9H, ArH's), 7.60 (d, 1H, J = 1.5 Hz pyrazole -5-CH), 13.11 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d6): δ 101.25, 125.31, 127.08, 127.30, 129.60, 129.64, 133.51, 138.44, 139.06, 141.43,

144.62; MS (*m/z*): 284 (M^+). (Found: C, 63.36; H, 4.25; N, 9.85; S, 11.28 $C_{15}H_{12}N_2O_2S$ requires C, 63.30; H, 4.27; N, 9.87; S, 11.29).

Synthesis of 2-amino-4-(4-(phenylsulfonyl)phenyl) Pyrimidine 5

Method A: under microwave irradiation

To an equimolar amount of enaminone **3** (0.315 g, 1mmol) and guanidine sulfate (1 mmol), 145 mg of K_2CO_3. The mixture was subjected to microwave irradiation (at 180 °C, 300 W) for 1h until completion of the reaction (monitored by TLC). The mixture was dissolved in hot CH_2Cl_2. the catalyst was removed by filtration and washed with hot CH_2Cl_2 and the solvent was evaporated under reduced pressure. The residue was purified by crystallization from ethanol to afford the pure product **5** in 95% yields.

Method B: under conventional Conditions

A solution of guanidine sulfate (1 mmol) in absolute ethanol (15 ml) was added to a stirred solution of the enaminone **3** (1 mmol) in boiling absolute ethanol (10 ml), stirring was continued for 20 min. This mixture was added to the appropriate K_2CO_3 (145 mg) in absolute ethanol (10 ml) and the reaction mixture was refluxed for 7 h. The solution was allowed to cool at room temperature and the precipitate was removed by filtration followed by concentration of the filtrate under reduced pressure. The solid products that formed was collected by filtration, washed with water and dried. Recrystallization from ethanol afforded **5** in 85% yields.

2-amino-4-(4-(phenylsulfonyl)phenyl)pyrimidine **(5).**
m.p.; 252-254°C; IR (KBr) υmax /cm^{-1}: 3453, 3158 (NH_2), 1563 (C=N), 1298, 1151 (SO_2); ^{1}H NMR (DMSO-d6): δ 6.82 (s, 2H, NH_2, D_2O exchangable), 7.15 (d, 1H, *J* = 5.1 Hz pyrimidine-6-CH), 7.61-8.35 (m, 9H, ArH's), 8.36 (d, 1H, *J* = 5.1 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d6): δ 106.43, 127.35, 127.78, 127.87, 129.76, 133.80, 140.76, 141.77, 142.25, 159.58, 161.65, 163.75; MS (*m/z*): 311 (M^+). (Found: C, 61.72; H, 4.21; N, 13.50; S, 10.30 $C_{16}H_{13}N_3O_2S$ requires C, 61.70; H, 4.20; N, 13.51; S, 10.31).

General procedure for the reaction of enaminone 3 with pyrazoles 6a-i

Method A: under microwave irradiation

An equimolar amount of *E*-3-(dimethylamino)-1-(4-(phenylsulfonyl)phenyl)prop-2-en-1-one **3** (0.315 g, 1mmol) and pyrazoles **6a-i** (1 mmol), in presence of catalytic amount of pyridine (0.25 ml), then the reaction mixture was subjected to microwave irradiation (at 180 °C, 300 W) for the appropriate time as listed in table 1 until consumption of reactants as determined by TLC. After cooling to room temperature, the residual solid was recrystallized from ethanol/DMF (1:1) to give pyrazolo[1,5-a]pyrimidine derivatives **8a-i**.

Method B: under conventional Conditions

To a mixture of enaminone **3** (0.315 g, 1mmol) and pyrazoles **6a-i** (1 mmol) in pyridine (25 ml). The reaction mixture was refluxed for 5h. The solid product was filtered off, washed with cold ethanol and recrystallized from ethanol/DMF to afford the pure products **8a-i**. The physical and spectral data of the synthesized compounds are listed below.

2-phenyl-7-(4-(phenylsulfonyl)phenyl)pyrazolo[1,5-a]pyrimidine **(8a).**
m.p.; 239-241°C; IR (KBr) υmax /cm^{-1}: 1599 (C=N), 1307, 1155 (SO_2); ^{1}H NMR (DMSO-d6): δ 7.31 (d, 1H, *J* = 4.2 Hz pyrimidine-6-CH), 7.38 (s, 1H, pyrazole-3-CH), 7.46-8.46 (m, 14H, ArH's), 8.63 (d, 1H, *J* = 4.5 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d6): δ 93.68, 108.64, 126.24, 127.39, 128.77, 129.08, 129.87, 130.76, 132.14, 134.04, 135.30, 140.45, 142.84, 143.29, 149.68, 150.46, 154.78; MS (*m/z*): 411 (M^+). Found: C, 70.05; H, 4.16; N, 10.21; S, 7.79 $C_{24}H_{17}N_3O_2S$ requires C, 70.02; H, 4.18; N, 10.21; S, 7.80).

2-(4-chlorophenyl)-7-(4-(phenylsulfonyl)phenyl) pyrazolo[1,5-a]pyrimidine **(8b).**
m.p.; 214-216°C; IR (KBr) υmax /cm–1: 1596 (C=N), 1317, 1158 (SO_2); ^{1}H NMR (DMSO-d6): δ 7.31 (d, 1H, *J* = 4.5 Hz pyrimidine-6-CH), 7.40 (s, 1H, pyrazole-3-CH), 7.51-8.44 (m, 13H, ArH's), 8.64 (d, 1H, *J* = 4.5 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d6): δ 93.92, 108.86, 127.42, 127.61, 127.92, 128.83, 129.88, 130.77, 131.06, 133.69, 134.05, 135.24, 143.36, 149.85, 153.56; MS (*m/z*): 445 (M^+). Found: C, 64.64; H, 3.62; N, 9.42; S, 7.19 $C_{24}H_{16}ClN_3O_2S$ requires C, 64.66; H, 3.60; N, 9.40; S, 7.21).

7-(4-(phenylsulfonyl)phenyl)-2-(4-methoxyphenyl) pyrazolo[1,5-a]pyrimidine **(8c).**
m.p.; 245-247°C ; IR (KBr) υmax /cm^{-1}: 1598 (C=N), 1306, 1156 (SO_2); ^{1}H NMR (DMSO-d6): δ 3.77 (s, 1H, OCH_3), 6.99 (d, 1H, *J* = 8.7 Hz pyrimidine-6-CH), 7.23 (s, 1H, pyrazole-3-CH), 7.61-8.56 (m, 13H, ArH's), 8.41 (d, 1H, *J* = 4.5 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d6): δ 55.45, 94.15, 110.87, 114.35, 127.84, 127.34, 128.12, 128.54, 129.17, 130.22, 132.15, 133.79, 134.50, 136.15, 138.24, 144.54, 146.04, 149.12, 155.04; MS (*m/z*): 441 (M^+). (Found: C, 68.01; H, 4.34; N, 9.52; S, 7.26

$C_{25}H_{19}N_3O_3S$ requires C, 68.03; H, 4.30; N, 9.50; S, 7.30).

2-methyl-3-phenyl-7-(4-(phenylsulfonyl)phenyl) pyrazolo[1,5-a]pyrimidine **(8d).**
m.p.; 260-262°C; IR (KBr) υmax /cm^{-1}: 1599 (C=N), 1310, 1153 (SO_2); ^{1}H NMR (DMSO-d6): δ 2.52 (s, 1H, CH_3), 7.24 (d, 1H, *J* = 4.2 Hz pyrimidine-6-CH), 7.31-8.31 (m, 14H, ArH's), 8.61 (d, 1H, *J* = 4.2 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d6): δ 14.09, 108.47, 120.49, 127.39, 127.57, 128.32, 128.58, 129.86, 130.72, 134.02, 135.44, 140.60, 142.80, 143.28, 146.54, 149.59, 149.60, 151.32,168.48; MS (*m/z*): 425 (M^+). (Found: C, 65.31; H, 4.33; N, 12.03; S, 9.18 $C_{25}H_{19}N_3O_2S$ requires C, 65.29; H, 4.35; N, 12.00; S, 9.21).

2-Amino-3-phenylazo-7-(4-(phenylsulfonyl)phenyl) pyrazolo[1,5-a]pyrimidine **(8e).**
m.p.; 223-225°C; IR (KBr) υmax /cm^{-1}: 3425, 2922 (NH_2), 1549 (C=N), 1310, 1157 (SO_2); ^{1}H NMR (DMSO-d6): 7.15 (s, 2H, NH_2, D_2O exchangeable), 7.27 (d, 1H, *J* = 4.5 Hz pyrimidine-6-CH), 7.45-8.34 (m, 14H, ArH's), 8.69 (d, 1H, *J* = 4.5 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d6): δ 109.31, 115.59, 120.45, 121.85, 126.34, 127.78, 129.57, 130.28, 133.15, 136.74, 139.24, 141.46, 142.96, 144.64, 148.68, 150.51, 151.54, 152.90 ; MS (*m/z*): 454 (M^+). (Found: C, 63.42; H, 3.99; N, 18.49; S, 7.05 $C_{24}H_{18}N_6O_2S$ requires C, 63.44; H, 4.01; N, 18.50; S, 7.01).

2-Amino-3-(4-methylphenylazo)-7-(4-(phenyl sulfonyl)phenyl)Pyrazolo[1,5-a]pyrimidine **(8f).**
m.p.; 260-262°C; IR (KBr) υmax /cm^{-1}: 3423, 2928 (NH_2), 1547 (C=N), 1305, 1154 (SO_2); ^{1}H NMR (DMSO-d6): δ 2.36 (s, 3H, CH_3), 7.12 (s, 2H, NH_2, D_2O exchangeable), 7.24 (d, 1H, *J* = 4.5 Hz pyrimidine-6-CH), 7.23-8.25 (m, 13H, ArH's), 8.62 (d, 1H, *J* = 4.5 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d6): δ 20.81, 109.38, 114.36, 120.60, 121.05, 127.28, 127.55, 129.55, 130.87, 134.02, 135.20, 138.33, 140.55, 142.83, 143.254, 147.34, 150.54, 150.90, 151.82 ; MS (m/z): 468 (M^+). (Found: C, 64.09; H, 4.30; N, 17.94; S, 6.84 $C_{25}H_{20}N_6O_2S$ requires C, 64.04; H, 4.32; N, 17.96; S, 6.85).

2-Amino-3-(4-methoxyphenylazo)-7-(4-(phenyl sulfonyl)phenyl)Pyrazolo[1,5-a]pyrimidine **(8g).**
m.p.; 230-232°C; IR (KBr) υmax /cm^{-1}: 3403, 3261 (NH_2), 1552 (C=N), 1302, 1153 (SO_2); ^{1}H NMR (DMSO-d6): δ 2.82 (s, 3H, OCH_3), 7.13 (s, 2H, NH_2, D_2O exchangeable), 7.04 (d, 1H, *J* = 4.5 Hz pyrimidine-6-CH), 7.21-8.58 (m, 13H, ArH's), 8.04 (d, 1H, *J* = 4.5 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d6): δ 55.38, 109.07, 114.08, 120.57, 123.82, 127.27, 129.87,134.02, 135.25, 136.04, 140.54, 142.80, 143.15, 147.09, 149.52, 150.35, 151.81, 153.03, 159.85; MS (*m/z*): 484 (M^+). (Found: C, 61.97; H, 4.16; N, 17.34; S, 6.62 $C_{25}H_{20}N_6O_2S$ requires C, 61.93; H, 4.17; N, 17.30; S, 6.63).

2-Amino-3-(4-fluorophenylazo)-7-(4-(phenyl sulfonyl)phenyl)pyrazolo[1,5-a]pyrimidine **(8h).**
m.p.; 250-252°C; IR (KBr) υmax /cm^{-1}: 3421, 3262 (NH_2), 1547 (C=N), 1315, 1149 (SO_2); 1H NMR (DMSO-d6): δ 7.20 (s, 2H, NH_2, D_2O exchangeable), 7.64 (d, 1H, *J* = 6.0 Hz pyrimidine-6-CH), 7.18-8.58 (m, 13H, ArH's), 8.14 (d, 1H, *J* = 6.0 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d6): δ 109.53, 114.53, 115.63, 122.97, 127.25, 129.54, 130.86, 135.12, 140.55, 142.84, 143.26, 147.44, 149.61, 150.58, 133.99, 151.79, 160.37, 163.63; MS (*m/z*): 472 (M^+). (Found: C, 61.01; H, 3.63; N, 17.79; S, 6.79 $C_{24}H_{17}FN_6O_2S$ requires C, 61.03; H, 3.65; N, 17.74; S, 6.80).

2-Amino-3-(4-bromophenylazo)-7-(4-(phenyl sulfonyl)phenyl)pyrazolo[1,5-a]pyrimidine **(8i).**
m.p.; 241-243°C; IR (KBr) υmax /cm^{-1}: 3418, 3287 (NH_2), 1545 (C=N), 1299, 1148 (SO_2); ^{1}H NMR (DMSO-d6): 7.20 (s, 2H, NH_2, D_2O exchangeable), 7.75 (d, 1H, *J* = 6.9 Hz pyrimidine-6-CH), 7.26-8.63 (m, 13H, ArH's), 8.96 (d, 1H, *J* = 6.9 Hz pyrimidine-5-CH); ^{13}C NMR (DMSO-d6): δ 109.89, 114.97, 120.58, 122.96, 127.94, 128.38, 129.78, 133.84, 134.03, 136.05, 140.90, 143.40, 146.24, 150.79, 131.96, 151.925, 152.87, 150.59; MS (*m/z*): 532 (M^+). (Found: C, 54.04; H, 3.21; N, 15.76; S, 6.01 $C_{24}H_{17}BrN_6O_2S$ requires C, 54.05; H, 3.20; N, 15.77; S, 6.00).4.

4. Conclusions

In conclusion, we have synthesized novel pyrazole, pyrimidine and fused pyrazolo[1,5-a]pyrimidines incorporating the aryl sulfone moiety under influence of microwave irradiation and conventional conditions. The clean protocol minimizes the organic solvent and energy demands, as well as, the reaction time could be reduced to a few minutes using MW irradiation and also this technique was found to be very useful to improve an overall yield and reaction selectivity.

Corresponding author:
Naglaa M. Abd El-Rahman
[1]Green Chemistry Department, National Research Centre, Dokki, Cairo, 12622, Egypt
[2]Chemistry department, Faculty of Science, Jazan University, Jazan, Saudi Arabia
naglaa_r@yahoo.com

References

1. (a) Julino, M.; Stevens, F. G. M. Antitumour polycyclic acridines. Part 5.1 Synthesis of 7H-pyrido[4,3,2-kl]acridines with exploitable functionality in the pyridine ring. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1677-1684; (b) Abdou, I. M.; Saleh, A. M.; Zohdi, H. F. Synthesis and antitumor activity of 5-trifluoromethyl-2,4-dihydropyrazol-3-one nucleosides. *Molecules* **2004,** *9*, 109-116.
2. El-Feky, S. A.; Abd el-Samii, Z. K. Synthesis and antihypertensive activity of novel 1-(4-benzyl-1-phthalazinyl)-pyrazolo[3,4-d]. pyrimidines. *Pharmazie* **1996**, *51*, 540-543.
3. (a) Davies, L. P.; Brown, D. J.; Chow, S. C.; Johnston, G. A. Pyrazolo[3,4-d] pyrimidines, a new class of adenosine antagonists. *Neurosci. Lett.* **1983**, *41*, 189-193; (b) Davies, L. P.; Chow, S. C.; Skerritt, J. H.; Brown, D. J.; Johnston, G. A., Pyrazolo[3,4-d]pyrimidines as adenosine antagonists. *Life Sci.* **1984**, **34**, 2117-2128.
4. Ghorab, M. M.; Ismail, Z. H.; Abdel-Gawad, S. M.; Abdel Aziem, A. Antimicrobial activity of amino acid, imidazole, and sulfonamide derivatives of pyrazolo[3,4-d]pyrimidine. *Heteroatom Chem.* **2004**, *15*, 57-62.
5. Holla, B. S.; Mahalinga, M.; Karthikeyan, M. S.; Akberali, P. M.; Shetty, N. S. Synthesis of some novel pyrazolo[3,4-d]pyrimidine derivatives as potential antimicrobial agents. *Bioorg. Med. Chem.* **2006,***14*, 2040-2047.
6. Gupta, S.; Rodrigues, L. M.; Esteves, A. P.; Oliveira-Campos, A. M.; Nascimento, M. S.; Nazareth, N.; Cidade, H.; Neves, M. P.; Fernandes, E.; Pinto, M.; Cerqueira, N. M.; Bras, N. Synthesis of N-aryl-5-amino-4-cyanopyrazole derivatives as potent xanthine oxidase inhibitors. *Eur. J. Med. Chem.* **2008,** *43*, 771-780.
7. Tamta, H.; Thilagavathi, R.; Chakraborti, A. K.; Mukhopahyay, A. K. 6-(N-benzoylamino)purine as a novel and potent inhibitor of xanthine oxidase: inhibition mechanism and molecular modeling studies. *J. Enzyme Inhib. Med. Chem.* **2005,** *20*, 317-324.
8. Bouabdallah, I.; M'Barek, L. A.; Zyad, A.; Ramdani, A.; Zidane, I.; Melhaoui, A. Anticancer effect of three pyrazole derivatives. *Nat. Prod. Res.* **2006,** *20*, 1024-1030.
9. Coimbra, C.; Boris-Moller, F.; Drake, M.; Wieloch, T. Diminished neuronal damage in the rat brain by late treatment with the antipyretic drug dipyrone or cooling following cerebral ischemia. *Acta Neuropathol.* **1996,** *92*, 447-453.
10. (a) Shaaban, M. R.; Saleh, T. S.; Mayhoub, A. S.; Mansour, A.; Farag, A. M. Synthesis and analgesic/anti-inflammatory evaluation of fused heterocyclic ring systems incorporating phenylsulfonyl moiety. *Bioorg. Med. Chem.* **2008,** *16*, 6344-6352; (b) Shaaban, M. R.; Saleh, T. S.; Mayhoub, A. S.; Farag, A. M. Single step synthesis of new fused pyrimidine derivatives and their evaluation as potent Aurora-A kinase inhibitors. *Eur. J. Med. Chem.* **2011,** *46*, 3690-3695.
11. Otzen, T.; Wempe, E. G.; Kunz, B.; Bartels, R.; Lehwark-Yvetot, G.; Hansel, W.; Schaper, K. J.; Seydel, J. K. Folate-synthesizing enzyme system as target for development of inhibitors and inhibitor combinations against Candida albicans-synthesis and biological activity of new 2,4-diaminopyrimidines and 4'-substituted-4-aminodiphenyl sulfones. *J. Med. Chem.* **2004,** *47*, 240-253.
12. Sun, Z. Y.; Botros, E.; Su, A. D.; Kim, Y.; Wang, E.; Baturay, N. Z.; Kwon, C. H. Sulfoxide-containing aromatic nitrogen mustards as hypoxia-directed bioreductivecytotoxins. *J. Med. Chem.* **2000,** *43*, 4160-4168.
13. Neamati, N.; Mazumder, A.; Zhao, H.; Sunder, S.; Burke, T. R., Jr.; Schultz, R. J.; Pommier, Y. Diarylsulfones, a novel class of human immunodeficiency virus type 1 integrase inhibitors. *Antimicrob. Agents Chemother.* **1997,** *41*, 385-93.
14. Doherty, G. A.; Kamenecka, T.; McCauley, E.; Van Riper, G.; Mumford, R. A.; Tong, S.; Hagmann, W. K. N-aryl 2,6-dimethoxybiphenylalanine analogues as VLA-4 antagonists. *Bioorg. Med. Chem. Lett.* **2002,** *12*, 729-731.
15. Clemett, D.; Goa, K. L. Celecoxib: a review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs* **2000,** *59*, 957-980.
16. Bing, R. J.; Lomnicka, M. Why do cyclo-oxygenase-2 inhibitors cause cardiovascular events? *J. Am. Coll. Cardiol.* **2002,** *39*, 521-522.
17. Sikes, D. H.; Agrawal, N. M.; Zhao, W. W.; Kent, J. D.; Recker, D. P.; Verburg, K. M. Incidence of gastroduodenal ulcers associated with valdecoxib compared with that of ibuprofen and diclofenac in patients with osteoarthritis. *Eur. J. Gastroenterol. Hepatol.* **2002,** *14*, 1101-1111.
18. Langman, M. J.; Jensen, D. M.; Watson, D. J.; Harper, S. E.; Zhao, P. L.; Quan, H.; Bolognese, J. A.; Simon, T. J. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* **1999,** *282*, 1929-1933.
19. Cochrane, D. J.; Jarvis, B.; Keating, G. M. Etoricoxib. *Drugs* **2002,** *62*, 2637-2651; discussion 2652-2653.

20. Dallob, A.; Hawkey, C. J.; Greenberg, H.; Wight, N.; De Schepper, P.; Waldman, S.; Wong, P.; DeTora, L.; Gertz, B.; Agrawal, N.; Wagner, J.; Gottesdiener, K. Characterization of etoricoxib, a novel, selective COX-2 inhibitor. *J. Clin. Pharmacol.* **2003,** *43*, 573-585.
21. Todd, P. A.; Clissold, S. P. Tenoxicam. An update of its pharmacology and therapeutic efficacy in rheumatic diseases. *Drugs* **1991,** *41*, 625-646.
22. Lee, C. R.; Balfour, J. A. Piroxicam-beta-cyclodextrin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in rheumatic diseases and pain states. *Drugs* **1994,** *48*, 907-929.
23. Fleischmann, R.; Iqbal, I.; Slobodin, G. Meloxicam. *Expert Opin. Pharmacother.* **2002,** *3*, 1501-1512.
24. Zhao, H.; Ye, T. H.; Gong, Z. Y.; Xue, Y.; Xue, Z. G.; Huang, W. Q. Application of lornoxicam to patient-controlled analgesia in patients undergoing abdominal surgeries. *Chin. Med. Sci. J.* **2005,** *20*, 59-62.
25. Kurumaji, Y., Ampiroxicam-induced photosensitivity. *Contact Dermatitis* **1996,** *34*, 298-299.
26. Bernareggi, A. Clinical pharmacokinetics of nimesulide. *Clin. Pharmacokinet.* **1998,** *35*, 247-274.
27. Abd El-Rahman, N. M.; El-Kateb, A. A.; Mady, M. F. Simplified approach to the uncatalyzedknoevenagel condensation and michael addition reactions in water using microwave irradiation. *Synth. Commun.* **2007**, *37*, 3961-3970.
28. Campo, C. J.; Tato, V. P. M.; Seijas, A. J. Microwave-Promoted, One-Pot, Solvent-Free Synthesis of 4-Arylcoumarins from 2-Hydroxybenzophenones. *Eur. J. Org. Chem.* **2010**, 4130–4135.
29. Abd El-Rahman, N. M.; Saleh, T. S.; Mady, M. F. Ultrasound assisted synthesis of some new 1,3,4-thiadiazole and bi(1,3,4-thiadiazole) derivatives incorporating pyrazolone moiety. *Ultrason. Sonochem.* **2009,** *16*, 70-74.
30. Saleh, T. S.; Abd El-Rahman, N. M. Ultrasound promoted synthesis of substituted pyrazoles and isoxazoles containing sulphone moiety. *Ultrason. Sonochem.* **2009,** *16*, 237-242.
31. Saleh, T. S.; Eldebss, T. M.; Albishri, H. M., Ultrasound assisted one-pot, three-components synthesis of pyrimido[1,2-a]benzimidazoles and pyrazolo[3,4-b]pyridines: A new access via phenylsulfonesynthon. *Ultrason. Sonochem.* **2012,** *19*, 49-55.
32. Fischer, P.; Schweizer, E.; Langner, J.; Schmidt, U. ^{13}C, ^{1}H long-range coupling constants in configuration assignment of some trisubstituted alkenes. *Magn. Reson. Chem.* **1994**, *32*, 567–568.
33. Al-Mousawi, S. M.; El-Apasery, M. A.; Elnagdi, M. H. Enaminones in heterocyclic synthesis: a novel route to tetrahydropyrimidines, dihydropyridines, triacylbenzenes and naphthofurans under microwave irradiation. *Molecules* **2010,** *15*, 58-67.
34. Stanovnik, B.; Svete, J. Synthesis of heterocycles from alkyl 3-(dimethylamino)propenoates and related enaminones. *Chem. Rev.* **2004,** *104*, 2433-2480.
35. Novinson, T.; Hanson, R.; Dimmitt, M. K.; Simon, L. N.; Robins, R. K.; O'Brien, D. E. 3-Substituted- 5,7-dimethylpyrazolo(1,5-a) pyrimidines, 3',5'-cyclic-AMP phosphodiesterase inhibitors. 1. *J. Med. Chem.* **1974,** *17*, 645-648.
36. Zou, J.; Li, F.; Tao, F. G. Microwave-assisted synthesis of diaryl or aryl-alkyl sulfones without catalyst. *Chin. Chem. Lett.* **2009**, *20,* 17-20.
37. Hori, I.; Igarashi, M. The Paal-Knorr Condensation of Acetonylacetone with 5-Aminopyrazoles. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2856-2858.
38. Elfahham, H. A.; Sadek, K. U.; Elgemeie, G. E. H.; Elnagdi, M. H. Novel synthesis of pyrazolo[5,1-c]-1,2,4-triazoles, imidazo[1,2-b]pyrazoles, and [1,2,4]-triazolo[4,3-a]benzimidazoles. Reaction of nitrite imines with amino- and oxo-substituted diazoles. *J. Chem. Soc. Perkin Trans. 1* **1982**, 2663-2666.

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