Synthesis of Some 6,8-Diarylimidazo[1,2-*a*]pyrazine Derivatives by Using Either Reflux or Microwave Irradiation Method and Investigation of Their Anticancer Activities

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Received June 22, 2004

In order to obtain some 6,8-diarylimidazo[1,2-*a*]pyrazines, 1-(2-aryl-2-oxoethyl)-2-aryloylimidazole derivatives were reacted with ammonium acetate in acetic acid by using a new method different from that found in the literature. Anticancer activities of the compounds obtained were evaluated and the noticeable activity values were reported.

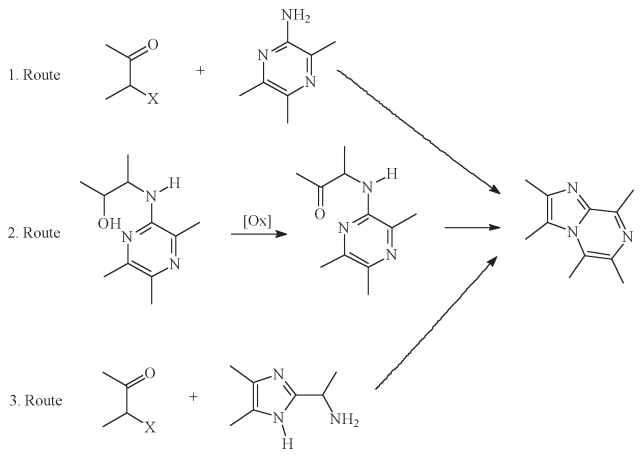
J. Heterocyclic Chem., **42**, 319 (2005).

The importance of imidazo[1,2-*a*]pyrazines [1] stems from their remarkable anticancer [2-7] and antimicrobial [8] activities in addition to their antihypertensive [9-11], antibroncospastic [12-14] and inotropic [12,15-20] activities on the cardiovascular system. The cause of great attention on these structures can be attributed to the fact that the chemiluminescent compounds, such as *Luciferin*, from some *Cypridina*, *Renilla*, *Oplophorus* and *Watasenia* species are imidazo[1,2-*a*]pyrazine derivatives [21-29].

Motivated by the above observations and as an extension of our previous work on pyrazino[1,2-*a*]benzimidazoles [30] which are structural analogue of imidazo[1,2-*a*]-pyrazines and show notable anticancer activities, especially on leucemia, we report here the synthesis and anticancer activity testing of some 6,8-diarylimidazo[1,2-*a*]-pyrazine derivatives.

Three general synthetic methods have been used for the formation of imidazo[1,2-*a*]pyrazine ring system in the literature; these are outlined in Scheme 1. The first method involves reactions between 2-aminopyrazine and α-functional carbonyl compounds [31-34]. In the second method, intermediate compounds obtained from 2-halopyrazine and an aminoethanol have been oxidized to give α-pyrazine-2-ylaminoethanone, followed by ring closure [21-29]. In the third method, 2-(aminomethyl)imidazoles have been reacted with an α-halocarbanyl compound [35-37].

Scheme 1



Synthesis of imidazo[1,2-a]pyrazine reported in the literature

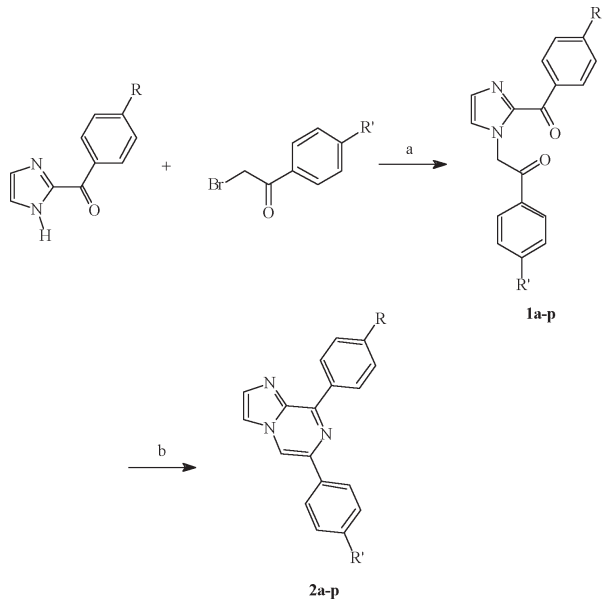
In this study, a new method different from three methods mentioned above was used for the formation of the imidazo[1,2-*a*]pyrazine ring system. 2-Aryloylimidazole derivatives were taken as starting materials. These compounds reacted with ω-bromoacetophenone to give 1-(2-aryl-2-oxoethyl)-2-aryloylimidazoles, **1a-p**. To obtaine 6,8-diarylimidazo[1,2-*a*]pyrazines, **2a-p**, the diketo compounds were reacted with ammonium acetate in acetic acid. The reaction was carried out by using either the classical reflux [30,38] or microwave irradiation method [39-46]. The synthesis is outlined in Scheme 2.

It was demonstrated that many organic reactions can be conducted very rapidly under microwave irradiation. This method has been preferred due to high reaction rates, cleaner products and operational symplicity. In this alternative reaction condition no product could be obtained in the absence of solvent. Thus, a small amount of acetic acid was used for solvating the substrates and microwave energy transfer.

In the IR spectra, carbonyl stretching bands, which are characteristic for compounds **1a-p**, were observed at about 1708-1685 cm^{-1} and 1645-1622 cm^{-1} regions. These two groups of carbonyl stretching bands are not observed after cyclization to give imidazo[1,2-*a*]pyrazine ring system.

In the NMR spectra, methylene protons resonated in alyphatic area at 6 ppm for **1a-p**. After cyclization, however, the corresponding proton resonances were shifted to the aromatic region in **2a-p** and observed at 9,2 ppm as singlets. Although, in this type of bicyclic system, frequently as small coupling constant (J 1 Hz) is observe between the protons at position 3 and position 5, this coupling was not observed in this study. Other characteristic peaks are due to the protons at position 4 and 5 of the imidazole residue for compounds **1a-p** and at positions 2 and 3 in imidazo[1,2-*a*]pyrazine ring system for compounds **2a-p**. The protons at position 4 and 5 in imidazole res-

Scheme 2



Reagents: a: K_2CO_3, CH_3COCH_3; b: CH_3COONH_4, CH_3COOH

	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**
R	H	H	H	H	CH_3	CH_3	CH_3	CH_3	OCH_3
R'	H	CH_3	OCH_3	Cl	H	CH_3	OCH_3	Cl	H

	j	**k**	**l**	**m**	**n**	**o**	**p**
R	OCH_3	OCH_3	OCH_3	Cl	Cl	Cl	Cl
R'	CH_3	OCH_3	Cl	H	CH_3	OCH_3	Cl

onated at 7.6 ppm and 7.3 ppm; after cyclization, the corresponding protons were shifted downfield and resonated at 7.9 ppm and 8.2 ppm. The protons mentioned above are expected to couple with J 0.8-2.5 Hz [47], however this small coupling constant, J 1 Hz, was observed only in some cases, but not for all.

Anticancer Activity.

The compounds selected by NCI and their preliminary anticancer test results as growth percent values obtained against CC, NSCLC and CNSC cells are given in Table 1. The compounds **2j**, **2m-p** having remarkable inhibition values were accepted for the further screening test. In this step, the selected five compounds were evaluated *in vitro* against sixty six human tumour cell lines derived from nine neoplastic diseases (see experimental section) and the detailed test results are given in Table 2.

According to the test method, it is stated that compounds having $\log_{10} GI_{50}$ (GI_{50}: growth inhibition of 50%) values greater than –4 are considered as inactive. It can be seen that all of our compounds' $\log_{10} GI_{50}$ values are smaller than –4. Therefore, we may conclude that all of our

Table 1

The Preliminary Test Results

Compounds	Conc. (Molar)	The growth percent BC MCF7	NSCLC NCI-H460	CNS SF-268
1c	$1x10^{-4}$	91	71	84
1d	$1x10^{-4}$	98	85	99
1g	$1x10^{-4}$	93	100	101
1h	$1x10^{-4}$	89	89	100
1i	$1x10^{-4}$	96	103	99
1l	$1x10^{-4}$	99	103	102
1m	$1x10^{-4}$	102	110	98
1o	$1x10^{-4}$	90	104	87
1p	$5x10^{-5}$	94	105	93
2c	$5x10^{-5}$	67	54	88
2d	$5x10^{-5}$	116	69	94
2g	$5x10^{-5}$	108	71	95
2h	$5x10^{-5}$	96	37	100
2i	$5x10^{-5}$	115	73	97
2j	$5x10^{-5}$	39	20	87
2l	$5x10^{-5}$	84	80	90
2m	$5x10^{-5}$	34	1	37
2n	$5x10^{-5}$	60	5	92
2o	$5x10^{-5}$	51	15	77
2p	$5x10^{-5}$	54	9	90

compounds provide a notable activity level. Melphalan and Cisplatin (*cis*-diaminodichloroplatinum) are two of standard compounds commonly used as chemotherapeutic agents. When the meangraph midpoint (MG-MID) values of the compounds Melphalan and Cisplatin, *i.e.* –5.09 and –6.20 respectively, are considered, it is observed that our compounds provide high activity levels. The MG-MID value of the compound **2n** is lower than that of the control compound Cisplatin. In a similar manner, the activity values of compounds **2j**, **2m-o** are higher than that of the other control compound Melphalan. When these data are examined according to their activity against various cancer types, it is observed that both the standard and the tested compounds are effective against leukaemia in lower concentrations, for all of the compounds this value is lower than –5. The most noteworthy compound is **2n**, which is even more active than melphalan against leukaemia. It is noticeable that all of the compounds, except **2j**, under detailed investigation carry 8-(4-chlorophenyl) group.

EXPERIMENTAL

Melting points were determined by using an Electrothermal 9100 Digital Melting Point Apparatus and are uncorrected. Spectroscopic data were recorded on the following instruments: IR, Shimadzu 8400 FTIR Spectrophotometer; ^{1}H-NMR; Bruker DPX 400 MHz NMR Spectrometer; MS; Agilent 1100 MSD Mass Spectrometer. 2-Aryloylimidazole[48] and ω-bromoacetophenone [49] derivatives were prepared according to literature methods.

Table 2

Log_{10} GI_{50} values

Compounds	L	NSCLC	CC	CNSC	M	OC	RC	PC	BC	MG_MID
2j	-5.61	-5.09	-5.45	-5.30	-5,30	-4.99	-5.14	-5.28	-5.13	-5.25
2m	-5.55	-4,68	-5.22	-5.01	-4.85	-4.90	-5.23	-4.89	-5.67	-5.10
2n	-7.10	-5.47	-6.62	-6.62	-6.27	-5.98	-6.34	-6.30	-6.58	-6.29
2o	-5.44	-4.90	-5.10	-4.93	-5.05	-5.07	-5.01	-4.89	-5.31	-5.07
2p	-6.20	-4.59	-5.04	-4.60	-4.68	-4.56	-4.88	-4.66	-4.92	-4.88
A	-5.48	-5.17	-5.11	-5.12	-5.08	-5.18	-4.99	-4.49	-4.79	-5.09
B	-6.39	-6.20	-6.14	-6.18	-6.08	-6.45	-6.17	-6.41	-6.05	-6.20

A: Melphalan, **B**: Cisplatin.

General Procedure for the Synthesis of 1-(2-Aryl-2-oxoethyl)-2-aryloylimidazoles (**1a-p**).

A mixture of a suitable 2-aryloylimidazole (5 mmol), ω-bromoacetophenone (5 mmol) and potassium carbonate (5 mmol) in acetone (50 ml) was stirred at room temperature. Stirring was continued at room temperature until the disappearance of the starting material was observed (4-6 h, TLC analyses). The solvent was evaporated at low temperature. The residue was washed with water and then ethanol. The raw product was recrystallised from ethanol.

1-(2-Phenyl-2-oxoethyl)-2-benzoylimidazole (**1a**).

This compound was prepared according to the general procedure above in a yield of 85%, mp 146-147°; ir (potassium bromide): 1703, 1635 (C=O), 1595-1448 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.11 (s, 2H), 7.33 (s, 1H, imidazole C_5-H), 7.50-7.54 (m, 2H), 7.61-7.66 (m, 4H), 7.73-7.77 (m, 1H), 8.09 (d, 2H, J = 8.34 Hz), 8.24 (d, 2H, J = 8.43 Hz); ms: (100 eV, electron spray) m/z 291 (molecular ion).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.13; H, 4.69; N, 9.64.

1-[2-(4-Methylphenyl)-2-oxoethyl]-2-benzoylimidazole (**1b**).

This compound was prepared according to the general procedure above in a yield of 90%, mp 158-159°; ir (potassium bromide): 1703, 1645 (C=O), 1604-1465 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.44 (s, 3H), 6.07 (s, 2H), 7.31 (s, 1H, imidazole C_5-H), 7.43 (d, 2H, J = 8.36 Hz), 7.50-7.54 (m, 2H), 7.62-7.66 (m, 2H), 7.98 (d, 2H, J = 8.19 Hz), 8.23 (d, 2H, J = 9.67 Hz).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.82; H, 5.38; N, 9.36.

1-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-benzoylimidazole (**1c**).

This compound was prepared according to the general procedure above in a yield of 84%, mp 182-183°; ir (potassium bromide): 1697, 1639 (C=O), 1602-1465 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.89 (s, 3H), 6.05 (s, 2H), 7.14 (d, 2H, J = 8.87 Hz), 7.30 (s, 1H, imidazole C_5-H), 7.50-7.54 (m, 2H), 7.61-7.66 (m, 2H), 8.06 (d, 2H, J = 8.85 Hz), 8.23 (dd, 2H, J = 1.39, 0.71, 7.89 Hz).

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.75. Found: C, 70.99; H, 4.90; N, 8.44.

1-[2-(4-Chlorophenyl)-2-oxoethyl]-2-benzoylimidazole (**1d**).

This compound was prepared according to the general procedure above in a yield of 88%, mp 183-184°; ir (potassium bromide): 1708, 1639 (C=O), 1589-1465 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.09 (s, 2H), 7.32 (s, 1H, imidazole C_5-H), 7.50-7.54 (m, 2H), 7.61-7.64 (m, 2H), 7.71 (d, 2H, J = 8.57 Hz), 8.10 (d, 2H, J = 8.54 Hz), 8.23 (dd, 2H, J = 1.37, 0.79, 8.43 Hz).

Anal. Calcd. for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.04; N, 8.63. Found: C, 66.45; H, 4.16; N, 8.51.

1-(2-Phenyl-2-oxoethyl)-2-(4-methylbenzoyl)imidazole (**1e**).

This compound was prepared according to the general procedure above in a yield of 89%, mp 158-159°; ir (potassium bromide): 1703, 1629 (C=O), 1606-1461 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.39 (s, 3H), 6.09 (s, 2H), 7.31-7.34 (m, 3H), 7.60-7.64 (m, 3H), 7.73-7.77 (m, 1H), 8.08 (d, 2H, J = 8.31 Hz), 8.19 (d, 2H, J = 8.16 Hz).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 75.74; H, 4.35; N, 9.30. Found: C, 75.56; H, 4.28; N, 9.54.

1-[2-(4-Methylphenyl)-2-oxoethyl]-2-(4-methylbenzoyl)imidazole (**1f**).

This compound was prepared according to the general procedure above in a yield of 83%, mp 153-154°; ir (potassium bromide): 1703, 1643 (C=O), 1604-1463 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.39 (s, 3H), 2.43 (s, 3H), 6.10 (s, 2H), 7.30 (s, 1H, imidazole C_5-H), 7.32 (d, 2H, J = 8.20 Hz), 7.43 (d, 2H, J = 8.13 Hz), 7.59 (s, 1H, imidazole C_4-H), 7.97 (d, 2H, J = 8.03 Hz), 8.18 (d, 2H, J = 8.08 Hz); ms: (100 eV, electron spray) m/z 335 (molecular ion).

Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.22; H, 5.68; N, 8.77. Found: C, 75.62; H, 5.36; N, 8.59.

1-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-(4-methylbenzoyl)imidazole (**1g**).

This compound was prepared according to the general procedure above in a yield of 86%, mp 189-190°; ir (potassium bromide): 1697, 1632 (C=O), 1602-1463 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.39 (s, 3H), 3.88 (s, 3H), 6.02 (s, 2H), 7.13 (d, 2H, J = 8.84 Hz), 7.29 (s, 1H, imidazole C_5-H), 7.32 (d, 2H, J = 8.19 Hz), 7.59 (s, 1H, imidazole C_4-H), 8.05 (d, 2H, J = 8.82 Hz), 8.19 (d, 2H, J = 8.19 Hz).

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.78; H, 5.62; N, 8.12.

1-[2-(4-Chlorophenyl)-2-oxoethyl]-2-(4-methylbenzoyl)imidazole (**1h**).

This compound was prepared according to the general procedure above in a yield of 87%, mp 166-167°; ir (potassium bro-

mide): 1697, 1635 (C=O), 1604-1461 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.39 (s, 3H), 6.07 (s, 2H), 7.31 (d, 1H, J = 0.91 Hz, imidazole C_5-H), 7.33 (d, 2H, J = 8.01 Hz), 7.59 (d, 1H, J = 0.60 Hz, imidazole C_4-H), 8.09 (d, 2H, J = 8.69 Hz), 8.19 (d, 2H, J = 8.23 Hz).

Anal. Calcd. for $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.65; H, 4.42; N, 8.14.

1-(2-Phenyl-2-oxoethyl)-2-(4-methoxybenzoyl)imidazole (**1i**).

This compound was prepared according to the general procedure above in a yield of 88%, mp 158-159°; ir (potassium bromide): 1706, 1627 (C=O), 1595-1461 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.85 (s, 3H), 6.08 (s, 2H), 7.05 (d, 2H, J = 8.79 Hz), 7.30 (s, 1H, imidazole C_5-H), 7.58-7.64 (m, 1H), 7.73-7.76 (m, 1H), 8.08 (d, 2H, J = 8.05 Hz), 8.34 (d, 2H, J = 8.87 Hz).

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.75. Found: C, 71.45; H, 5.24; N, 8.46.

1-[2-(4-Methylphenyl)-2-oxoethyl]-2-(4-methoxybenzoyl)-imidazole (**1j**).

This compound was prepared according to the general procedure above in a yield of 83%, mp 161-162°; ir (potassium bromide): 1685, 1631 (C=O), 1601-1461 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.43 (s, 3H), 3.85 (s, 3H), 6.04 (s, 2H), 7.05 (d, 2H, J = 8.90 Hz), 7.29 (s, 1H, imidazole C_5-H), 7.42 (d, 2H, J = 8.17 Hz), 7.57 (s, 1H, imidazole C_4-H), 7.97 (d, 2H, J = 8.15 Hz), 8.33 (d, 2H, J = 8.84 Hz).

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.02; H, 5.67; N, 8.45.

1-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-(4-methoxybenzoyl)-imidazole (**1k**).

This compound was prepared according to the general procedure above in a yield of 87%, mp 192-193°; ir (potassium bromide): 1695, 1622 (C=O), 1600-1420 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.85 (s, 3H), 3.88 (s, 3H), 6.02 (s, 2H), 7.05 (d, 2H, J = 9.02 Hz), 7.13 (d, 2H, J = 8.92 Hz), 7.28 (s, 1H, imidazole C_5-H), 7.56 (s, 1H, imidazole C_4-H), 8.05 (d, 2H, J = 8.91 Hz), 8.33 (d, 2H, J = 8.99 Hz).

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.46; H, 5.11; N, 8.57.

1-[2-(4-Chlorophenyl)-2-oxoethyl]-2-(4-methoxybenzoyl)-imidazole (**1l**).

This compound was prepared according to the general procedure above in a yield of 89%, mp 195-196°; ir (potassium bromide): 1697, 1629 (C=O), 1601-1460 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.85 (s, 3H), 6.06 (s, 2H), 7.05 (d, 2H, J = 9.02 Hz), 7.29 (s, 1H, imidazole C_5-H), 7.57 (s, 1H, imidazole C_4-H), 7.71 (d, 2H, J = 8.60 Hz), 8.09 (d, 2H, J = 8.62 Hz), 8.34 (d, 2H, J = 8.98 Hz).

Anal. Calcd. for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.87; H, 4.05; N, 7.84.

1-(2-Phenyl-2-oxoethyl)-2-(4-chlorobenzoyl)imidazole (**1m**).

This compound was prepared according to the general procedure above in a yield of 89%, mp 157-158°; ir (potassium bromide): 1703, 1631 (C=O), 1587-1464 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.06 (s, 2H), 7.34 (s, 1H, imidazole C_5-H), 7.59 (s, 1H, imidazole C_4-H), 7.61-7.64 (m, 4H), 7.73-7.77 (m, 1H), 8.08 (d, 2H, J = 7.54 Hz), 8.29 (d, 2H, J = 8.51 Hz).

Anal. Calcd. for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.04; N, 8.63. Found: C, 66.42; H, 4.26; N, 8.54.

1-[2-(4-Methylphenyl)-2-oxoethyl]-2-(4-chlorobenzoyl)imidazole (**1n**).

This compound was prepared according to the general procedure above in a yield of 83%, mp 165-166°; ir (potassium bromide): 1699, 1633 (C=O), 1606-1458 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.43 (s, 3H), 6.07 (s, 2H), 7.33 (s, 1H, imidazole C_5-H), 7.43 (d, 2H, J = 8.08 Hz), 7.60 (d, 2H, J = 8.63 Hz), 7.64 (s, 1H, imidazole C_4-H), 7.98 (d, 2H, J = 8.18 Hz), 8.29 (d, 2H, J = 8.61 Hz); ms: (100 eV, electron spray) m/z 339 (molecular ion).

Anal. Calcd. for $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.65; H, 4.12; N, 8.26.

1-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-(4-chlorobenzoyl)imidazole (**1o**).

This compound was prepared according to the general procedure above in a yield of 85%, mp 178-179°; ir (potassium bromide): 1693, 1633 (C=O), 1603-1458 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.89 (s, 3H), 6.04 (s, 2H), 7.14 (d, 2H, J = 8.83 Hz), 7.32 (s, 1H, imidazole C_5-H), 7.60 (d, 2H, J = 8.57 Hz), 7.63 (s, 1H, imidazole C_4-H), 8.05 (d, 2H, J = 8.82 Hz), 8.29 (d, 2H, J = 8.60 Hz).

Anal. Calcd. for $C_{19}H_{15}ClN_2O_2$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.74; H, 4.64; N, 7.58.

1-[2-(4-Chlorophenyl)-2-oxoethyl]-2-(4-chlorobenzoyl)imidazole (**1p**).

This compound was prepared according to the general procedure above in a yield of 87%, mp 199-200°; ir (potassium bromide): 1697, 1635 (C=O), 1587-1458 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.09 (s, 2H), 7.34 (s, 1H, imidazole C_5-H), 7.60 (d, 2H, J = 8.64 Hz), 7.63 (s, 1H, imidazole C_4-H), 7.71 (d, 2H, J = 8.58 Hz), 8.10 (d, 2H, J = 8.62 Hz), 8.29 (d, 2H, J = 8.67 Hz).

Anal. Calcd. for $C_{18}H_{12}Cl_2N_2O_2$: C, 60.19; H, 3.37; N, 7.80. Found: C, 60.23; H, 3.42; N, 7.74.

General Procedure for the Synthesis of 6,8-Diarylimidazo[1,2-*a*]-pyrazines (**2a-p**).

Method A.

A solution of suitable **1a-p** (3 mmol) and ammonium acetate (30 mmol) in 50 mL of acetic acid was refluxed for 3 h. The solution was cooled, poured into ice water and neutralised with sodium carbonate. The precipitate that formed was collected by filtration and crystallised in ethanol.

Method B.

A mixture of suitable **1a-p** (1 mmol) and ammonium acetate (10 mmol) in 0.5 mL of acetic acid was placed in a 25 mL erlenmayer flask and covered with a watch glass. The mixture was irradiated at power 600 W in a domestic microwave oven for 40-45 sec. Work-up is as described under Method A.

6,8-Diphenylimidazo[1,2-*a*]pyrazine (**2a**).

This compound was prepared according to the general procedures above in yields of 78% for Method A and 82% for Method B, mp 144-145°; ir (potassium bromide): 1600-1473 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.42-7.46 (m, 1H), 7.53-7.67 (m, 5H), 7.92 (s, 1H, imidazopyrazine C_3-H), 8.16 (d, 2H, J = 8.32 Hz), 8.21 (s, 1H, imidazopyrazine C_2-H), 8.92 (d, 2H, J = 8.11

Hz), 9.24 (s, 1H, imidazopyrazine C_5-H); ms: (35 eV, electron spray) m/z 272 (molecular ion).

Anal. Calcd. for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49. Found: C, 79.54; H, 4.89; N, 15.57.

6-(4-Methylphenyl)-8-phenylimidazo[1,2-*a*]pyrazine (**2b**).

This compound was prepared according to the general procedures above in yields of 80% for Method A and 88% for Method B, mp 118-119°; ir (potassium bromide): 1652-1479 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.38 (s, 3H), 7.35 (d, 2H, J = 8.03 Hz), 7.57-7.63 (m, 3H), 7.90 (d, 1H, J = 1.00 Hz, imidazopyrazine C_3-H), 8.05 (d, 2H, J = 8.18 Hz), 8.20 (d, 1H, imidazopyrazine C_2-H), 8.91 (dd, 2H, J = 1.41, 1.80, 8.10 Hz), 9.21 (s, 1H, imidazopyrazine C_5-H).

Anal. Calcd. for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.72. Found: C, 79.84; H, 5.46; N, 14.70.

6-(4-Methoxyphenyl)-8-phenylimidazo[1,2-*a*]pyrazine (**2c**).

This compound was prepared according to the general procedures above in yields of 81% for Method A and 86% for Method B, mp 142-143°; ir (potassium bromide): 1604-1483 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.83 (s, 3H), 7.11 (d, 2H, J = 8.86 Hz), 7.56-7.63 (m, 3H), 7.89 (d, 1H, J = 0.90 Hz, imidazopyrazine C_3-H), 8.10 (d, 2H, J = 8.85 Hz), 8.18 (d, 1H, J = 0.90 Hz, imidazopyrazine C_2-H), 8.91 (dd, 2H, J = 1.40, 1.80, 8.11 Hz), 9.14 (s, 1H, imidazopyrazine C_5-H).

Anal. Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.58; H, 5.16; N, 13.79.

6-(4-Chlorophenyl)-8-phenylimidazo[1,2-*a*]pyrazine (**2d**).

This compound was prepared according to the general procedures above in yields of 77% for Method A and 81% for Method B, mp 147-148°; ir (potassium bromide): 1600-1475 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.57-7.62 (m, 5H), 7.92 (s, 1H, imidazopyrazine C_3-H), 8.19 (d, 2H, J = 8.57 Hz), 8.22 (s, 1H, imidazopyrazine C_2-H), 8.91 (dd, 2H, J = 1.29, 1.73, 7.84 Hz), 9.31 (s, 1H, imidazopyrazine C_5-H); ms: (100 eV, electron spray) m/z 306 (molecular ion).

Anal. Calcd. for $C_{18}H_{12}ClN_3$: C, 70.73; H, 4.27; N, 13.70. Found: C, 70.85; H, 4.31; N, 13.65.

6-Phenyl-8-(4-methylphenyl)imidazo[1,2-*a*]pyrazine (**2e**).

This compound was prepared according to the general procedures above in yields of 76% for Method A and 84% for Method B, mp 121-122°; ir (potassium bromide): 1600-1473 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.42 (s, 3H), 7.40-7.46 (m, 3H), 7.53-7.57 (m, 2H), 7.89 (s, 1H, imidazopyrazine C_3-H), 8.16 (d, 2H, J = 8.09 Hz), 8.20 (s, 1H, imidazopyrazine C_2-H), 8.86 (d, 2H, J = 7.82 Hz), 9.22 (s, 1H, imidazopyrazine C_5-H).

Anal. Calcd. for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.72. Found: C, 79.85; H, 5.38; N, 14.77.

6,8-Di(4-methylphenyl)imidazo[1,2-*a*]pyrazine (**2f**).

This compound was prepared according to the general procedures above in yields of 76% for Method A and 80% for Method B, mp 164-165°; ir (potassium bromide): 1610-1479 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.38 (s, 3H), 2.42 (s, 3H), 7.35 (d, 2H, J = 8.08 Hz), 7.40 (d, 2H, J = 8.18 Hz), 7.88 (d, 1H, J = 0.89 Hz, imidazopyrazine C_3-H), 8.04 (d, 2H, J = 8.18 Hz), 8.17 (d, 1H, J = 0.90 Hz, imidazopyrazine C_2-H), 8.85 (d, 2H, J = 8.26 Hz), 9.16 (s, 1H, imidazopyrazine C_5-H); ms: (35 eV, electron spray) m/z 300 (molecular ion).

Anal. Calcd. for $C_{20}H_{17}N_3$: C, 80.24; H, 5.72; N, 14.04. Found: C, 80.14; H, 5.68; N, 14.18.

6-(4-Methoxyphenyl)-8-(4-methylphenyl)imidazo[1,2-*a*]pyrazine (**2g**).

This compound was prepared according to the general procedures above in yields of 75% for Method A and 78% for Method B, mp 137-138°; ir (potassium bromide): 1606-1481 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.42 (s, 3H), 3.83 (s, 3H), 7.10 (d, 2H, J = 8.87 Hz), 7.40 (d, 2H, J = 8.13 Hz), 7.87 (d, 1H, J = 0.95 Hz, imidazopyrazine C_3-H), 8.08 (d, 2H, J = 8.85 Hz), 8.15 (d, 1H, J = 0.96 Hz, imidazopyrazine C_2-H), 8.84 (d, 2H, J = 8.84 Hz), 9.10 (s, 1H, imidazopyrazine C_5-H).

Anal. Calcd. for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.24; H, 5.36; N, 13.25.

6-(4-Chlorophenyl)-8-(4-methylphenyl)imidazo[1,2-*a*]pyrazine (**2h**).

This compound was prepared according to the general procedures above in yields of 76% for Method A and 82% for Method B, mp 160-161°; ir (potassium bromide): 1600-1477 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.41 (s, 3H), 7.39 (d, 2H, J = 8.14 Hz), 7.59 (d, 2H, J = 8.61 Hz), 7.89 (d, 1H, J = 0.91 Hz, imidazopyrazine C_3-H), 8.15 (s, 1H, imidazopyrazine C_2-H), 8.17 (8.84 (d, 2H, J = 6.68 Hz), 8.85 (d, 2H, J = 8.26 Hz), 9.24 (s, 1H, imidazopyrazine C_5-H).

Anal. Calcd. for $C_{19}H_{14}ClN_3$: C, 71.36; H, 4.41; N, 13.14. Found: C, 71.45; H, 4.28; N, 13.31.

6-Phenyl-8-(4-methoxyphenyl)imidazo[1,2-*a*]pyrazine (**2i**).

This compound was prepared according to the general procedures above in yields of 78% for Method A and 88% for Method B, mp 89-90°; ir (potassium bromide): 1606-1454 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.88 (s, 3H), 7.16 (d, 2H, J = 8.81 Hz), 7.42-7.46 (m, 1H), 7.53-7.57 (m, 2H), 7.88 (s, 1H, imidazopyrazine C_3-H), 8.15 (s, 1H, imidazopyrazine C_2-H), 8.18 (d, 2H, J = 8.01 Hz), 8.96 (d, 2H, J = 8.75 Hz), 9.19 (s, 1H, imidazopyrazine C_5-H).

Anal. Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.66; H, 5.11; N, 13.88.

6-(4-Methylphenyl-8-(4-methoxyphenyl)imidazo[1,2-*a*]pyrazine (**2j**).

This compound was prepared according to the general procedures above in yields of 76% for Method A and 82% for Method B, mp 95-96°; ir (potassium bromide): 1606-1481 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.38 (s, 3H), 3.87 (s, 3H), 7.15 (d, 2H, J = 8.96 Hz), 7.35 (d, 2H, J = 8.00 Hz), 7.87 (s, 1H, imidazopyrazine C_3-H), 8.05 (d, 2H, J = 8.07 Hz), 8.16 (s, 1H, imidazopyrazine C_2-H), 8.95 (d, 2H, J = 8.92 Hz), 9.14 (s, 1H, imidazopyrazine C_5-H).

Anal. Calcd. for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.26; H, 5.38; N, 13.44.

6,8-Di(4-methoxyphenyl)imidazo[1,2-*a*]pyrazine (**2k**).

This compound was prepared according to the general procedures above in yields of 75% for Method A and 84% for Method B, mp 101-102°; ir (potassium bromide): 1605-1481 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.83 (s, 3H), 3.87 (s, 3H), 7.11 (d, 2H, J = 8.64 Hz), 7.16 (d, 2H, J = 8.77 Hz), 7.86 (s, 1H, imida-

zopyrazine C_3-H), 8.08 (d, 2H, J = 8.62 Hz), 8.13 (s, 1H, imidazopyrazine C_2-H), 8.95 (d, 2H, J = 8.89 Hz), 9.07 (s, 1H, imidazopyrazine C_5-H).

Anal. Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.58; H, 5.24; N, 12.46.

6-(4-Chlorophenyl)-8-(4-methoxyphenyl)imidazo[1,2-*a*]-pyrazine (**2l**).

This compound was prepared according to the general procedures above in yields of 77% for Method A and 82% for Method B, mp 76-77°; ir (potassium bromide): 1600-1450 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.87 (s, 3H), 7.14 (d, 2H, J = 8.94 Hz), 7.59 (d, 2H, J = 8.56 Hz), 7.88 (s, 1H, imidazopyrazine C_3-H), 8.15-8.18 (m, 3H), 8.94 (d, 2H, J = 8.95 Hz), 9.19 (s, 1H, imidazopyrazine C_5-H); ms: (35 eV, electron spray) m/z 336 (molecular ion).

Anal. Calcd. for $C_{19}H_{14}ClN_3O$: C, 61.47; H, 3.80; N, 11.32. Found: C, 61.41; H, 3.88; N, 11.39.

6-Phenyl-8-(4-chlorophenyl)imidazo[1,2-*a*]pyrazine (**2m**).

This compound was prepared according to the general procedures above in yields of 88% for Method A and 91% for Method B, mp 144-145°; ir (potassium bromide): 1589-1477 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.43-7.46 (m, 1H), 7.53-7.57 (m, 2H), 7.67 (d, 2H, J = 8.59 Hz), 7.92 (s, 1H, imidazopyrazine C_3-H), 8.16 (d, 2H, J = 7.51 Hz), 8.22 (s, 1H, imidazopyrazine C_2-H), 8.99 (d, 2H, J = 8.59 Hz), 9.26 (s, 1H, imidazopyrazine C_5-H).

Anal. Calcd. for $C_{18}H_{12}ClN_3$: C, 70.71; H, 5.17; N, 13.74. Found: C, 70.62; H, 5.23; N, 13.86.

6-(4-Methylphenyl-8-(4-chlorophenyl)imidazo[1,2-*a*]pyrazine (**2n**).

This compound was prepared according to the general procedures above in yields of 89% for Method A and 87% for Method B, mp 136-137°; ir (potassium bromide): 1589-1479 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.38 (s, 3H), 7.35 (d, 2H, J = 8.06 Hz), 7.67 (d, 2H, J = 8.59 Hz), 7.90 (s, 1H, imidazopyrazine C_3-H), 8.03 (d, 2H, J = 8.06 Hz), 8.19 (s, 1H, imidazopyrazine C_2-H), 8.98 (d, 2H, J = 8.61 Hz), 9.20 (s, 1H, imidazopyrazine C_5-H).

Anal. Calcd. for $C_{19}H_{14}ClN_3$: C, 71.36; H, 4.41; N, 13.14. Found: C, 71.48; H, 4.56; N, 13.26.

6-(4-Methoxyphenyl-8-(4-chlorophenyl)imidazo[1,2-*a*]pyrazine (**2o**).

This compound was prepared according to the general procedures above in yields of 95% for Method A and 95% for Method B, mp 132-133°; ir (potassium bromide): 1606-1479 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.84 (s, 3H), 7.11 (d, 2H, J = 8.77 Hz), 7.67 (d, 2H, J = 8.64 Hz), 7.90 (s, 1H, imidazopyrazine C_3-H), 8.09 (d, 2H, J = 8.73 Hz), 8.19 (s, 1H, imidazopyrazine C_2-H), 8.99 (d, 2H, J = 8.62 Hz), 9.16 (s, 1H, imidazopyrazine C_5-H).

Anal. Calcd. for $C_{19}H_{14}ClN_3O$: C, 67.96; H, 4.20; N, 12.51. Found: C, 67.88; H, 4.12; N, 12.42.

6,8-Di(4-chlorophenyl)imidazo[1,2-*a*]pyrazine (**2p**).

This compound was prepared according to the general procedures above in yields of 88% for Method A and 90% for Method B, mp 118-119°; ir (potassium bromide): 1600-1475 (C=C, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.61 (d, 2H, J = 8.54 Hz), 7.67 (d, 2H, J = 8.64 Hz), 7.93 (s, 1H, imidazopyrazine C_3-H), 8.17 (d, 2H, J = 8.58 Hz),8.22 (s, 1H, imidazopyrazine C_2-H), 8.98 (d, 2H, J = 8.63 Hz), 9.30 (s, 1H, imidazopyrazine C_5-H); ms: (50 eV, electron spray) m/z 340 (molecular ion).

Anal. Calcd. for $C_{18}H_{11}Cl_2N_3$: C, 63.55; H, 3.26; N, 12.35. Found: C, 63.68; H, 3.15; N, 12.48.

Anticancer Activity Tests.

The cytotoxic and/or growth inhibitory effects of the compounds were evaluated *in vitro* against approximately sixty six human tumour cell lines derived from nine neoplastic diseases namely; Leukaemia (L), Non-Small Cell Lung Cancer (NSCLC), Colon Cancer (CC), Central Nervous System Cancer (CNSC), Melanoma (M), Ovarian Cancer (OC), Renal Cancer (RC), Prostate Cancer (PC), Breast Cancer (BC). The evaluation of anticancer activity was performed at the National Cancer Institute (NCI) of Bethesda, USA, following the *in vitro* screening program, which is based upon the use of multiple panels of 66 human tumour cell lines against which our compounds were tested at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8} *M*. The percentage growth was evaluated spectrophotometrically versus controls not treated with test agents. A 48 h continuous drug exposure protocol was followed and a sulforhodamine B (SRB) protein assay was used to estimate cell viability of growth [50].

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