



## Short communication

## Microwave supported synthesis of some novel 1,3-Diarylpyrazino[1,2-a]benzimidazole derivatives and investigation of their anticancer activities

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## ABSTRACT

The syntheses of 1,3-diarylpyrazino[1,2-a]benzimidazole derivatives and the investigation of their anticancer activities were studied. For this, 2-aryloylbenzimidazole derivatives were reacted with 2-bromoacetophenones in acetone to give 1-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles. The resulting materials were reacted with ammonium acetate in acetic acid to obtain the aimed compound. In this reaction, microwave irradiation method was applied as the reaction conditions. Anticancer activities of the compounds obtained were investigated. It was observed that some of the compounds showed remarkable anticancer activities.

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## 1. Introduction

Cancer is the worldwide health problem and the most frightening disease of human. In the present study we have concentrated on identified numerous chemical substances, as we have done in some our earlier publications [1–3], aiming to design the novel antitumor reagents [4].

The importance of imidazo[1,2-a]pyrazines [5] stems especially from their remarkable anticancer [6–10] and antimicrobial activities [11] along with antihypertensive [12,13], antibronchospastic [14,15] and inotropic activities [16,17] on the cardiovascular system.

Motivated by the above observations and as an extension of our previous works on imidazo[1,2-a]pyrazine [2] and pyrazino[1,2-a]benzimidazole [3,18] which exhibited remarkable anticancer activities especially on leukemia, we now report on the synthesis and the anticancer activity testing of some 2,3,6,8-tetraarylimidazo[1,2-a]pyrazine derivatives.

## 2. Chemistry

Some novel 1,3-diarylpyrazino[1,2-a]benzimidazole derivatives were synthesized and their structures were elucidated by analytical and spectroscopic methods. 2-Aryloylbenzimidazole derivatives were taken as starting materials. These compounds were reacted with

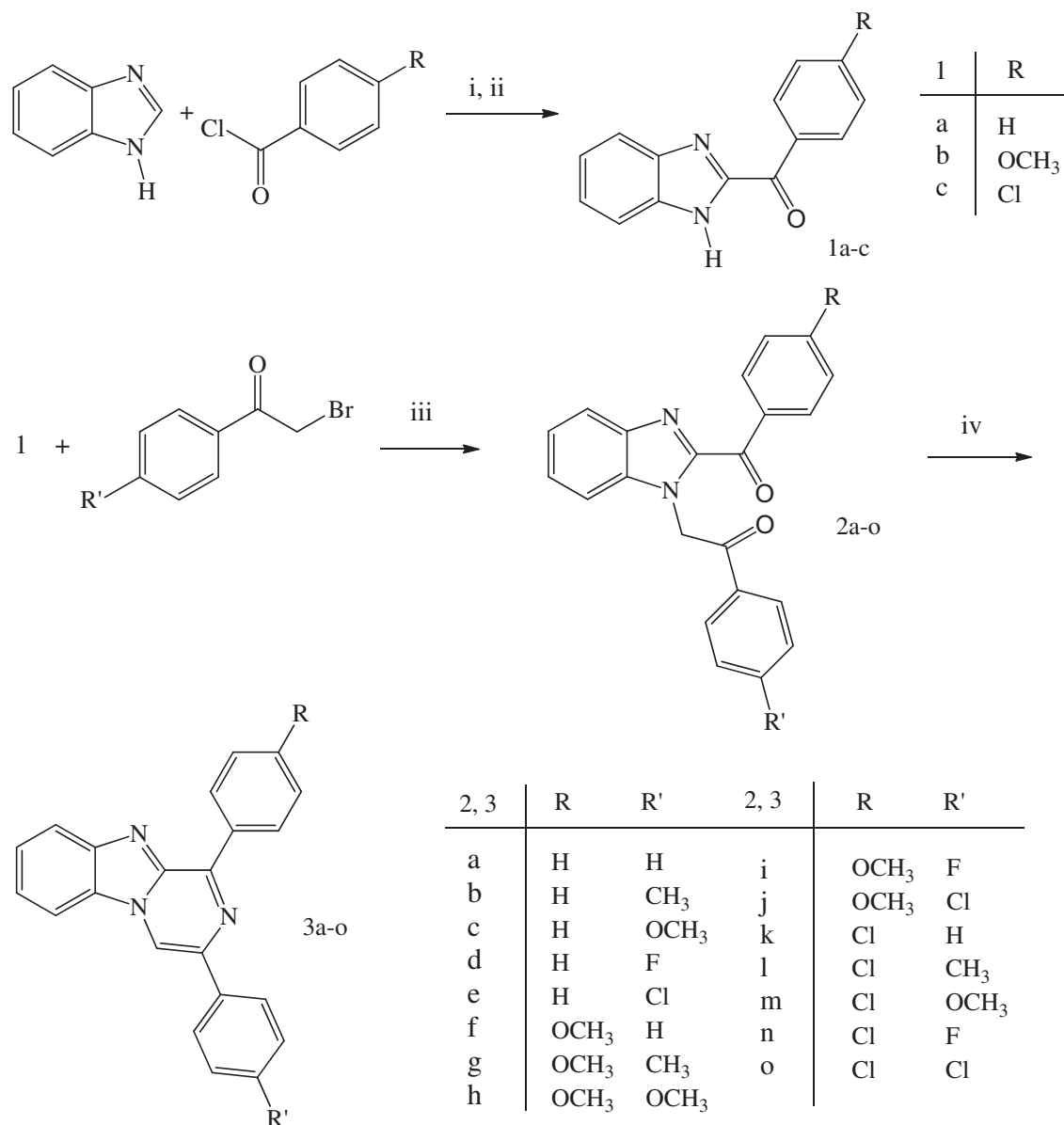
2-bromoacetophenones to afford 1-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles, **2a–o**. To obtain 1,3-diarylpyrazino[1,2-a]benzimidazole derivatives, **3a–o**, the diketone derivatives **2a–o** were reacted with ammonium acetate in a minimum amount of acetic acid by using microwave irradiation [2,19] as a facile synthetic method. The synthesis pathway of compounds was outlined in Scheme 1. It was demonstrated that many organic reactions can be conducted very rapidly under microwave irradiation. This method was preferred due to high reaction rates, purer products and operational simplicity. 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 solving the substrates and microwave energy transfer.

In the IR spectra, carbonyl stretching bands, which are characteristic for the compounds **2a–p**, were observed at about 1708–1685 cm<sup>-1</sup> and 1645–1632 cm<sup>-1</sup> regions. These two groups of carbonyl stretching bands disappeared after cyclization to give pyrazino[1,2-a]benzimidazole ring system.

In the NMR spectra, methylene protons resonated in aliphatic area at 6.3 ppm for **2a–o**. After cyclization, however, the corresponding protons were shifted to the aromatic area in **3a–o** and observed at 9.6 ppm as singlets. Other characteristic peaks due to the aromatic protons were observed as expected.

In the MS spectra, the electron spraying technique with positive polarity mode was applied and M + 1 peaks were detected as base peak.

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**Scheme 1.** Reagents and conditions; (i)  $(C_2H_5)_3N$ , pyridine, stirring at RT; (ii) NaOH,  $H_2O$ , reflux; (iii)  $K_2CO_3$ ,  $CH_3COCH_3$ , stirring at RT; (iv)  $CH_3COONH_4$ ,  $CH_3COOH$ , MW irradiation, 2 min.

### 3. Results and discussion

In the first step, the compounds **2a–e**, **2h–j**, **2m**, **2o**, **3a–f**, **3j** and **3l** were selected by NCI for the anticancer tests. The selected compounds were tested in vitro against sixty human tumor cell lines derived from nine neoplastic diseases and the test results were determined as growth percent values for  $10^{-5}$  M concentration. The obtained growth percent values were depicted in Table 1.

The remarkable low growth percent values were obtained for the compounds **2c** and **2h** against leukaemia cell lines as  $-3.26$  and  $-2.92\%$  respectively. With respect to mean values, the compound **2h** exhibited the lowest growth percent value with 25.51%. The compounds **2c**, **2e** and **2j** also possessed remarkable growth values. As the test method requires, the compounds having growth percent lower than 75% were accepted for the further screening test. Thus, **2a**, **2c–e**, **2h**, **2j** and **2m** which are diketone compounds were taken into the second stage. In this step, the selected compounds were

tested at 10-fold dilutions of five concentrations (100, 10, 1, 0.1 and 0.01  $\mu M$ ). The results were given as  $\log_{10} GI_{50}$  ( $GI_{50}$ : growth inhibition of 50%). The detailed test results are given in Table 2.

The test method states that the compounds having  $\log_{10} GI_{50}$  values greater than  $-4$  are considered as inactive. It can be seen that for all compounds the  $\log_{10} GI_{50}$  values are smaller than  $-4$ . Therefore, we may conclude that all of our compounds under investigation provide a notable activity level. melphalan and cisplatin (cis-diaminodichloroplatinum) are two of the commonly used chemotherapeutic agents and used as standard compounds. When the mean graph 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 values of the compound **2c–e**, **2h** and **2j** are lower than that of the control compound melphalan. In this respect, **2c** and **2h** are remarkable compounds with the MG-MID values,  $-5.54$  and  $-5.46$  respectively. The activity levels of the compounds bearing methoxy or halogen are higher than that of the

**Table 1**  
Anticancer activity of the compounds as % growth.

Compounds	L	NSCLC	CC	CNSC	M	OC	RC	PC	BC	Mean
<b>2a</b>	52.17	82.55	68.71	82.33	75.38	87.00	86.38	86.50	58.75	71.95
<b>2b</b>	70.50	91.01	72.24	101.15	72.07	80.45	85.16	91.45	80.51	82.73
<b>2c</b>	-3.26	36.00	22.43	25.38	31.26	30.25	38.60	33.20	23.32	28.08
<b>2d</b>	29.98	70.39	48.96	65.49	46.46	65.25	71.58	87.42	48.89	48.89
<b>2e</b>	21.67	52.44	40.14	37.17	34.13	44.33	45.13	34.00	9.00	35.87
<b>2h</b>	-2.92	38.33	19.69	23.85	26.74	27.87	35.98	44.39	18.28	25.51
<b>2i</b>	71.48	101.01	71.24	106.10	68.06	84.42	97.16	93.45	81.51	85.89
<b>2j</b>	3.41	51.54	33.14	23.44	24.15	29.51	43.77	35.08	28.82	31.68
<b>2m</b>	35.89	73.04	52.38	67.11	51.48	64.17	63.14	83.57	59.95	59.77
<b>2o</b>	64.71	83.43	86.00	99.15	82.30	113.50	85.42	93.84	103.27	89.36
<b>3a</b>	93.67	100.25	89.17	62.17	86.29	61.50	101.17	91.50	85.14	85.76
<b>3b</b>	93.67	102.38	94.83	77.00	92.57	85.17	103.00	89.50	85.71	85.71
<b>3c</b>	90.00	95.39	98.10	103.74	102.86	102.35	96.67	106.57	85.34	97.47
<b>3d</b>	98.77	92.59	105.96	91.16	109.13	91.34	91.75	95.32	88.78	95.15
<b>3e</b>	91.67	79.33	77.83	67.50	80.29	64.50	84.14	78.00	75.67	77.89
<b>3f</b>	101.82	91.43	99.96	93.98	94.95	87.71	95.17	102.30	88.87	94.33
<b>3j</b>	110.76	100.21	98.79	98.48	106.17	92.78	96.96	113.88	103.72	101.33
<b>3l</b>	106.68	110.69	97.43	128.36	105.13	94.06	108.81	104.20	98.47	106.47

first member of the series, i.e. **2a**. It is interesting to see that the more active compounds **2c** and **2h** bear methoxy group.

#### 4. Experimental protocols

##### 4.1. Chemistry

Melting points were determined by using an Electrothermal 9100 Digital Melting Point Apparatus. Spectroscopic data were recorded on the following instruments: IR, Shimadzu 8400 FTIR Spectrophotometer; <sup>1</sup>H NMR; Bruker DPX 500 MHz NMR Spectrometer. Microwave irradiated reactions were performed by using a Milestone Microsynth Apparatus. Compound **1a**, **2a,b,e**, **3a,b,e** were synthesized in an our previous study [3]. 2-bromoacetophenone derivatives [20] were prepared by using the reported literature methods.

##### 4.1.1. General procedure for 2-aryloylbenzimidazoles (**1b,c**)

Benzimidazole (100 mmol) was completely dissolved in pyridine (30 mL) then added triethylamine (28.4 mL). A suitable benzoylchloride (200 mmol) was gently and slowly dropped to the reaction media during the solution was stirred in ice bath under atmosphere with nitrogen gas. Then the mixture was stirred in room temperature without nitrogen atmosphere during a day. NaOH solution (7.5 N, 6 g NaOH and 20 mL water) was added to the mixture and refluxed for an hour. The reaction media was poured into ice-water and kept in a refrigerator for two days. The residue was filtered and washed with water. The raw product was recrystallized from ethanol.

##### 4.1.2. 2-(4-Methoxybenzoyl)benzimidazole (**1b**)

Yield: 55%. IR(KBr) $\nu_{\text{maks}}(\text{cm}^{-1})$ : 1652 (C=O), 1605–1510 (C=N and C=C), <sup>1</sup>H NMR(500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 3.88 (3H, s,

OCH<sub>3</sub>), 7.12 (2H, d, *J*: 8.8 Hz, Ar-H), 7.40–7.43 (1H, m, Ar-H), 7.47–7.5 (1H, m, Ar-H), 8.12 (2H, d, *J*: 8.78 Hz Ar-H), 11.40 (1H, bs, N-H). Anal. Calcd. for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>: C: 71.42, H: 4.79, N: 11.10. Found: C: 71.35, H: 5.01, N: 10.95.

##### 4.1.3. 2-(4-Chlorobenzoyl)benzimidazole (**1c**)

Yield: 62%. m.p. 224–226 °C. IR(KBr) $\nu_{\text{maks}}(\text{cm}^{-1})$ : 1648 (C=O), 1598–1490 (C=N and C=C), <sup>1</sup>H NMR(500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 7.41–7.44 (1H, m, Ar-H), 7.48–7.51 (1H, m, Ar-H), 7.69 (2H, *J*: 8.27 Hz, Ar-H), 8.32 (2H, d, *J*: 8.34 Hz, Ar-H), 11.45 (1H, bs, N-H). Anal. Calcd. for C<sub>14</sub>H<sub>9</sub>ClN<sub>2</sub>O: C: 65.51, H: 3.53, N: 10.91. Found: C: 65.27, H: 3.70, N: 11.02.

##### 4.1.4. General procedure for 1-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles (**2a–o**)

A mixture of the suitable 2-aryloylbenzimidazole (5 mmol), 2-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 (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 recrystallized from ethanol.

##### 4.1.5. 1-(2-(4-Methoxyphenyl)-2-oxoethyl)-2-benzoylbenzimidazole (**2c**)

Yield: 87%. m.p. 155–156 °C. IR(KBr) $\nu_{\text{maks}}(\text{cm}^{-1})$ : 1685, 1652 (C=O), 1605–1500 (C=N and C=C), 1282, 1216 (C–O–Ar), <sup>1</sup>H NMR (500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 3.90 (3H, s, OCH<sub>3</sub>), 6.26 (2H, s, CH<sub>2</sub>CO), 7.16 (2H, d, *J*: 8.94 Hz, Ar-H), 7.42 (1H, t, *J*: 7.12 Hz and 7.20 Hz, Ar-H), 7.48 (1H, t, *J*: 7.23 Hz and 7.20 Hz, Ar-H), 7.60 (2H, t, *J*: 7.57 Hz and 8.01 Hz, Ar-H), 7.72 (1H, t, *J*: 7.20 Hz and 7.24 Hz,

**Table 2**  
Log<sub>10</sub> GI<sub>50</sub> values of the selected compounds.

Compounds	L	NSCLC	CC	CNSC	M	OC	RC	PC	BC	MG_MID
<b>2a</b>	-4.28	-4.16	-4.2	-4.08	-4	-4	-4.06	-4.14	-5.03	-4.15
<b>2c</b>	-6.14	-5.03	-5.82	-5.40	-5.53	-5.44	-5.49	-5.49	-5.65	-5.54
<b>2d</b>	-5.85	-4.73	-5.45	-5.07	-5.34	-4.97	-5.56	-4.87	-5.40	-5.27
<b>2e</b>	-5.69	-4.74	-5.33	-5.88	-5.43	-5.05	-4.94	-5.37	-5.80	-5.25
<b>2h</b>	-6.13	-4.82	-5.90	-5.48	-5.49	-5.52	-5.41	-5.53	-5.62	-5.51
<b>2j</b>	-6.14	-4.84	-5.60	-5.47	-5.61	-5.28	-5.43	-5.52	-5.46	-5.46
<b>2m</b>	-5.59	-4.73	-5.30	-4.78	-5.02	-4.75	-4.85	-4.62	-5.21	-5.01
<b>A</b>	-5.48	-5.17	-5.11	-5.12	-5.08	-5.18	-4.99	-4.49	-4.79	-5.09
<b>B</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.

Ar–H), 7.85 (1H, d, *J*: 8.28 Hz, Ar–H), 7.93 (1H, d, *J*: 8.13 Hz), 8.12 (2H, d, *J*: 8.88 Hz, Ar–H), 8.28 (2H, d, *J*: 8.13 Hz, Ar–H). MS: (35 eV, electron spray) *m/z* 371.1 (*M* + 1, 100%), 372.0 (*M* + 2, 35%). Anal. Calcd. for C<sub>23</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>·H<sub>2</sub>O: C: 71.12, H: 5.13, N: 7.21. Found: C: 71.02, H: 4.90, N: 6.96.

#### 4.1.6. 1-(2-(4-Fluorophenyl)-2-oxoethyl)-2-benzoylbenzimidazole (**2d**)

Yield: 76%. m.p. 177–179 °C. IR(KBr) $\nu_{\text{maks}}$ (cm<sup>-1</sup>): 1700, 1638 (C=O), 1598–1480 (C=N and C=C), <sup>1</sup>H NMR(500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 6.31 (2H, s, CH<sub>2</sub>CO), 7.42 (1H, t, *J*: 7.47–7.51 (3H, m, Ar–H), 7.60 (2H, t, *J*: 7.47 Hz, Ar–H), 7.71–7.73 (1H, m, Ar–H), 7.86 (1H, d, *J*: 8.56 Hz, Ar–H), 7.94 (1H, d, *J*: 8.13 Hz), 8.24 (2H, dd, *J*: 8.89 Hz and 5.5 Hz, Ar–H), 8.28 (2H, d, *J*: 8.04 Hz, Ar–H). Anal. Calcd. for C<sub>22</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>2</sub>·H<sub>2</sub>O: C: 70.21, H: 4.55, N: 7.44. Found: C: 69.88, H: 4.32, N: 7.40.

#### 4.1.7. 1-(2-Phenyl-2-oxoethyl)-2-(4-methoxybenzoyl)benzimidazole (**2f**)

Yield: 68%. m.p. 218–220 °C. IR(KBr) $\nu_{\text{maks}}$ (cm<sup>-1</sup>): 1695, 1645 (C=O), 1590–1480 (C=N ve C=C), 1280, 1220 (C–O–Ar), <sup>1</sup>H NMR (500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 3.91 (3H, s, OCH<sub>3</sub>), 6.28 (2H, s, CH<sub>2</sub>CO), 7.42–7.62 (7H, m, Ar–H), 7.86 (1H, d, *J*: 8.56 Hz, Ar–H), 7.92 (1H, d, *J*: 8.13 Hz), 8.12 (2H, *J*: 8.58 Hz, Ar–H), 8.28 (2H, d, *J*: 8.25 Hz, Ar–H). Anal. Calcd. for C<sub>23</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>·H<sub>2</sub>O: C: 71.12, H: 5.19, N: 7.21. Found: C: 70.88, H: 5.10, N: 6.90.

#### 4.1.8. 1-(2-(4-Methylphenyl)-2-oxoethyl)-2-(4-methoxybenzoyl)benzimidazole (**2g**)

Yield: 72%. m.p. 172–173 °C. IR(KBr) $\nu_{\text{maks}}$ (cm<sup>-1</sup>): 1685, 1450 (C=O), 1602–1500 (C=N and C=C), 1288, 1218 (C–O–Ar), <sup>1</sup>H NMR (500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 2.45 (3H, s, CH<sub>3</sub>), 3.89 (3H, s, OCH<sub>3</sub>), 6.25 (2H, s, CH<sub>2</sub>CO), 7.13 (2H, d, *J*: 8.94 Hz, Ar–H), 7.40 (1H, t, *J*: 7.76 Hz and 7.77 Hz, Ar–H), 7.44–7.48 (3H, m, Ar–H), 7.83 (1H, d, *J*: 8.21 Hz), 7.92 (1H, d, *J*: 8.08 Hz, Ar–H), 8.03 (2H, d, *J*: 8.18 Hz Ar–H), 8.36 (2H, d, *J*: 8.94 Hz, Ar–H). Anal. Calcd. for C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>·H<sub>2</sub>O: C: 71.60, H: 5.51, N: 6.96. Found: C: 71.38, H: 5.50, N: 7.02.

#### 4.1.9. 1-(2-(4-Methoxyphenyl)-2-oxoethyl)-2-(4-methoxybenzoyl)benzimidazole (**2h**)

Yield: 66%. m.p. 180–181 °C. IR(KBr) $\nu_{\text{maks}}$ (cm<sup>-1</sup>): 1690, 1635 (C=O), 1597–1495 (C=N and C=C), 1290, 1232 (C–O–Ar) <sup>1</sup>H NMR (500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 3.89 (3H, s, OCH<sub>3</sub>), 3.90 (3H, s, OCH<sub>3</sub>), 6.23 (2H, s, CH<sub>2</sub>CO), 7.14 (4H, t, *J*: 9.1 Hz and 9.13 Hz, Ar–H), 7.40 (1H, t, *J*: 7.28 Hz, 7.76 Hz, Ar–H), 7.46 (1H, t, *J*: 7.81 Hz and 7.80 Hz, Ar–H), 7.82 (1H, d, *J*: 8.19 Hz), 7.92 (1H, d, *J*: 8.07 Hz, Ar–H), 8.11 (2H, d, *J*: 8.78 Hz Ar–H), 8.36 (2H, d, *J*: 8.78 Hz, Ar–H). Anal. Calcd. for C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>·2H<sub>2</sub>O: C: 66.04, H: 5.54, N: 6.42. Found: C: 65.88, H: 5.45, N: 6.77.

#### 4.1.10. 1-(2-(4-Fluorophenyl)-2-oxoethyl)-2-(4-methoxybenzoyl)benzimidazole (**2i**)

Yield: 75%. m.p. 213–214 °C. IR(KBr) $\nu_{\text{maks}}$ (cm<sup>-1</sup>): 1704, 1650 (C=O), 1612–1500 (C=N and C=C), 1282, 1220 (C–O–Ar) <sup>1</sup>H NMR (500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 3.92 (3H, s, OCH<sub>3</sub>), 6.23 (2H, s, CH<sub>2</sub>CO), 7.13 (2H, d, *J*: 8.76 Hz, Ar–H), 7.40 (1H, t, *J*: 7.28 Hz, 7.76 Hz, Ar–H), 7.46–7.52 (3H, m, Ar–H), 7.83 (1H, d, *J*: 8.20 Hz, Ar–H), 7.94 (1H, d, *J*: 8.17 Hz, Ar–H), 8.24 (2H, d, *J*: 8.68 Hz Ar–H), 8.37 (2H, d, *J*: 8.68 Hz, Ar–H). Anal. Calcd. for C<sub>23</sub>H<sub>17</sub>FN<sub>2</sub>O<sub>3</sub>·H<sub>2</sub>O: C: 67.97, H: 4.71, N: 6.89. Found: C: 67.85, H: 5.02, N: 6.90.

#### 4.1.11. 1-(2-(4-Chlorophenyl)-2-oxoethyl)-2-(4-methoxybenzoyl)benzimidazole (**2j**)

Yield: 77%. m.p. 184–186 °C. IR(KBr) $\nu_{\text{maks}}$ (cm<sup>-1</sup>): 1700, 1638 (C=O), 1599–1495 (C=N and C=C), 1288, 1223 (C–O–Ar) <sup>1</sup>H NMR

(500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 3.89 (3H, s, OCH<sub>3</sub>), 6.27 (2H, s, CH<sub>2</sub>CO), 7.13 (2H, d, *J*: 9.03 Hz, Ar–H), 7.41 (1H, t, *J*: 7.28 Hz and 7.76 Hz, Ar–H), 7.47 (1H, t, *J*: 7.77 Hz and 7.68 Hz, Ar–H), 7.73 (2H, d, *J*: 8.63 Hz, Ar–H), 7.84 (1H, d, *J*: 8.25 Hz, Ar–H), 7.93 (1H, d, *J*: 8.08 Hz, Ar–H), 8.15 (2H, d, *J*: 8.61 Hz Ar–H), 8.37 (2H, d, *J*: 8.98 Hz, Ar–H). MS: (35 eV, electron spray) *m/z* 405.1 (*M* + 1, 100%), 406.1 (*M* + 2, 8%), 407 (*M* + 3, 35%), 408 (*M* + 4, 10%). Anal. Calcd. for C<sub>23</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>3</sub>·H<sub>2</sub>O: C: 65.33, H: 4.53, N: 6.62. Found: C: 65.45, H: 4.52, N: 6.55.

#### 4.1.12. 1-(2-Phenyl-2-oxoethyl)-2-(4-chlorobenzoyl)benzimidazole (**2k**)

Yield: 82%. m.p. 223–226 °C. IR(KBr) $\nu_{\text{maks}}$ (cm<sup>-1</sup>): 1692, 1636 (C=O), 1603–1500 (C=N and C=C), <sup>1</sup>H NMR(500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 6.32 (2H, s, CH<sub>2</sub>CO), 7.42–7.62 (5H, m, Ar–H), 7.69 (2H, *J*: 8.27 Hz, Ar–H), 7.85 (1H, d, *J*: 8.68 Hz, Ar–H), 7.92 (1H, d, *J*: 8.53 Hz), 8.12 (2H, *J*: 8.58 Hz, Ar–H), 8.32 (2H, d, *J*: 8.34 Hz, Ar–H). Anal. Calcd. for C<sub>22</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>2</sub>·H<sub>2</sub>O: C: 67.26, H: 4.36, N: 7.13. Found: C: 67.11, H: 4.35, N: 7.00.

#### 4.1.13. 1-(2-(4-Methylphenyl)-2-oxoethyl)-2-(4-chlorobenzoyl)benzimidazole (**2l**)

Yield: 78%. m.p. 190–192 °C. IR(KBr) $\nu_{\text{maks}}$ (cm<sup>-1</sup>): 1706, 1646 (C=O), 1602–1598 (C=N and C=C), <sup>1</sup>H NMR(500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 2.44 (3H, s, CH<sub>3</sub>), 6.32 (2H, s, CH<sub>2</sub>CO), 7.42 (1H, t, *J*: 7.62 Hz, and 7.41 Hz, Ar–H), 7.46–7.52 (3H, m, Ar–H), 7.69 (2H, *J*: 8.05 Hz, Ar–H), 7.87 (1H, d, *J*: 8.23 Hz, Ar–H), 7.93 (1H, d, *J*: 8.19 Hz, Ar–H), 8.03 (2H, d, *J*: 8.27 Hz, Ar–H), 8.36 (2H, d, *J*: 8.02 Hz, Ar–H). Anal. Calcd. for C<sub>23</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>2</sub>·H<sub>2</sub>O: C: 67.90, H: 4.71, N: 6.89. Found: C: 68.10, H: 4.80, N: 6.90.

#### 4.1.14. 1-(2-(4-Methoxyphenyl)-2-oxoethyl)-2-(4-chlorobenzoyl)benzimidazole (**2m**)

Yield: 68%. m.p. 175–176 °C. IR(KBr) $\nu_{\text{maks}}$ (cm<sup>-1</sup>): 1698, 1632 (C=O), 1595–1490 (C=N ve C=C), 1278, 1218 (C–O–Ar), <sup>1</sup>H NMR (500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 3.90 (3H, s, OCH<sub>3</sub>), 6.25 (2H, s, CH<sub>2</sub>CO), 7.17 (2H, d, 8.94 Hz, Ar–H), 7.42 (1H, t, *J*: 7.62 Hz, and 7.41 Hz, Ar–H), 7.49 (1H, t, *J*: 7.18 Hz and 7.22 Hz, Ar–H), 7.69 (2H, *J*: 8.63 Hz, Ar–H), 7.86 (1H, d, *J*: 8.26 Hz, Ar–H), 7.93 (1H, d, *J*: 8.15 Hz, Ar–H), 8.11 (2H, d, *J*: 8.88 Hz, Ar–H), 8.33 (2H, d, *J*: 8.67 Hz, Ar–H). Anal. Calcd. for C<sub>23</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>3</sub>·H<sub>2</sub>O: C: 65.33, H: 4.53, N: 6.62. Found: C: 65.20, H: 4.44, N: 6.57.

#### 4.1.15. 1-(2-(4-Fluorophenyl)-2-oxoethyl)-2-(4-chlorobenzoyl)benzimidazole (**2n**)

Yield: 82%. m.p. 207–208 °C. IR(KBr) $\nu_{\text{maks}}$ (cm<sup>-1</sup>): 1688, 1634 (C=O), 1600–1496 (C=N and C=C), <sup>1</sup>H NMR(500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 3.90 (3H, s, OCH<sub>3</sub>), 6.25 (2H, s, CH<sub>2</sub>CO), 7.41 (1H, t, *J*: 7.62 Hz, and 7.46 Hz, Ar–H), 7.47–7.51 (3H, m, Ar–H), 7.69 (2H, *J*: 8.63 Hz, Ar–H), 7.86 (1H, d, *J*: 8.16 Hz, Ar–H), 7.93 (1H, d, *J*: 8.25 Hz, Ar–H), 8.24 (2H, d, *J*: 8.76 Hz, Ar–H), 8.34 (2H, d, *J*: 8.75 Hz, Ar–H). Anal. Calcd. for C<sub>22</sub>H<sub>14</sub>ClFN<sub>2</sub>O<sub>2</sub>·H<sub>2</sub>O: C: 64.32, H: 3.93, N: 7.13. Found: C: 64.30, H: 4.21, N: 7.44.

#### 4.1.16. 1-(2-(4-Chlorophenyl)-2-oxoethyl)-2-(4-chlorobenzoyl)benzimidazole (**2o**)

Yield: 85%. m.p. 186–188 °C. IR(KBr) $\nu_{\text{maks}}$ (cm<sup>-1</sup>): 1702, 1647 (C=O), 1601–1500 (C=N and C=C), <sup>1</sup>H NMR(500 MHz)(DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 6.30 (2H, s, CH<sub>2</sub>CO), 7.42 (1H, t, *J*: 7.62 Hz, and 7.41 Hz, Ar–H), 7.50 (1H, *J*: 8.05 Hz and 7.21 Hz, Ar–H), 7.68 (2H, d, *J*: 8.14 Hz, Ar–H), 7.73 (2H, d, *J*: 8.03 Hz, Ar–H), 7.87 (1H, d, *J*: 8.13 Hz, Ar–H), 7.94 (1H, d, *J*: 8.03 Hz, Ar–H), 8.16 (2H, d, *J*: 8.03 Hz, Ar–H), 8.34 (2H, d, *J*: 7.99 Hz, Ar–H). MS: (35 eV, electron spray) *m/z* 409 (*M* + 1, 100%), 410 (*M* + 2, 16%), 411 (*M* + 3, 42%), 412 (*M* + 4, 16%). Anal. Calcd. for C<sub>22</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>·2H<sub>2</sub>O: C: 61.62, H: 4.23, N: 6.53. Found: C: 61.45, H: 4.20, N: 6.42.

#### 4.1.17. General procedure for 1,3-diarylpyrazino[1,2-*a*]benzimidazoles (**3a–o**)

A mixture of suitable **2a–o** (1 mmol) and ammonium acetate (10 mmol) in 0.5 mL of acetic acid was irradiated at power 600 W in a Microwave Organic Synthesis Apparatus for 2 min. The solution was cooled, poured into ice-water and neutralized with sodium carbonate. The precipitate formed was filtered and crystallized in ethanol.

#### 4.1.18. 1-Phenyl-3-(4-methoxyphenyl)pyrazino[1,2-*a*]benzimidazole (**3c**)

Yield: 78%. m.p. 210–211 °C. IR(KBr) $\nu_{\text{maks}}$ ( $\text{cm}^{-1}$ ): 1606–1500 (C=N ve C=C), 1280, 1226 (C–O–Ar),  $^1\text{H NMR}$ (500 MHz)(DMSO- $d_6$ )  $\delta$  (ppm): 3.86 (3H, s, OCH<sub>3</sub>), 7.15 (2H, J: 8.95 Hz, Ar–H), 7.56–7.59 (1H, m, Ar–H), 7.60–7.63 (1H, m, Ar–H), 7.65–7.68 (2H, m, Ar–H), 8.06 (1H, J: 8.25 Hz, Ar–H), 8.28 (2H, d, J: 8.80 Hz, Ar–H), 8.60 (1H, d, J: 8.60 Hz, Ar–H), 9.03 (2H, d, J: 7.13 Hz, Ar–H), 9.67 (1H, s, Ar–H). MS: (35 eV, electron spray)  $m/z$  351.1 (M + 1, 100%), 352.1 (M + 2, 25%), 353 (M + 3, 12%). Anal. Calcd. for C<sub>23</sub>H<sub>17</sub>N<sub>3</sub>O: C: 78.61, H: 4.86, N: 11.96. Found: C: 78.56, H: 4.70, N: 11.78.

#### 4.1.19. 1-Phenyl-3-(4-fluorophenyl)pyrazino[1,2-*a*]benzimidazole (**3d**)

Yield: 75%. m.p. 214–216 °C. IR(KBr) $\nu_{\text{maks}}$ ( $\text{cm}^{-1}$ ): 1628–1508 (C=N and C=C),  $^1\text{H NMR}$ (500 MHz)(DMSO- $d_6$ )  $\delta$  (ppm): 7.35 (2H, t, J: 8.78 Hz, Ar–H), 7.50 (1H, t, J: 7.5 Hz, Ar–H), 7.55–7.59 (4H, m, Ar–H), 8.00 (1H, d, J: 8.23 Hz, Ar–H), 8.27 (2H, dd, J: 8.67 Hz and 5.52 Hz, Ar–H), 8.49 (1H, d, J: 8.25 Hz, Ar–H), 8.96 (2H, d, J: 8.19 Hz, Ar–H), 9.60 (1H, s, Ar–H). Anal. Calcd. for C<sub>22</sub>H<sub>14</sub>FN<sub>3</sub>: C: 77.86, H: 4.16, N: 12.38. Found: C: 77.80, H: 4.20, N: 12.00.

#### 4.1.20. 1-(4-Methoxyphenyl)-3-phenylpyrazino[1,2-*a*]benzimidazole (**3f**)

Yield: 72%. m.p. 245–247 °C. IR(KBr) $\nu_{\text{maks}}$ ( $\text{cm}^{-1}$ ): 1608–1505 (C=N and C=C), 1270, 1212 (C–O–Ar),  $^1\text{H NMR}$ (500 MHz)(DMSO- $d_6$ )  $\delta$  (ppm): 3.87 (3H, s, OCH<sub>3</sub>), 7.17 (2H, d, J: 8.90 Hz, Ar–H), 7.43 (1H, t, J: 7.31 Hz and J: 7.27 Hz, Ar–H), 7.51–7.56 (3H, m, Ar–H), 7.62 (1H, t, J: 7.61 Hz and J: 7.54 Hz, Ar–H), 8.03 (1H, d, J: 8.23 Hz, Ar–H), 8.27 (2H, d, J: 7.52 Hz, Ar–H), 8.54 (1H, d, J: 8.23 Hz, Ar–H), 9.04 (2H, d, J: 8.88 Hz, Ar–H), 9.60 (1H, s, Ar–H). Anal. Calcd. for C<sub>23</sub>H<sub>17</sub>N<sub>3</sub>O: C: 78.61, H: 4.86, N: 11.96. Found: C: 78.68, H: 4.57, N: 12.00.

#### 4.1.21. 1-(4-Methoxyphenyl)-3-(4-methylphenyl)pyrazino[1,2-*a*]benzimidazole (**3g**)

Yield: 68%. m.p. 240–241 °C. IR(KBr) $\nu_{\text{maks}}$ ( $\text{cm}^{-1}$ ): 1608–1500 (C=N and C=C), 1286, 1218 (C–O–Ar),  $^1\text{H NMR}$ (500 MHz)(DMSO- $d_6$ )  $\delta$  (ppm): 2.41 (3H, s, CH<sub>3</sub>), 3.91 (3H, s, OCH<sub>3</sub>), 7.22 (2H, J: 8.99 Hz, Ar–H), 7.39 (2H, d, J: 8.13 Hz, Ar–H), 7.55–7.58 (1H, m, Ar–H), 7.64–7.67 (1H, m, Ar–H), 8.06 (1H, J: 8.29 Hz, Ar–H), 8.22 (2H, d, J: 8.16 Hz, Ar–H), 8.59 (1H, d, J: 9.00 Hz), 9.08 (2H, d, J: 9.01 Hz, Ar–H), 9.65 (1H, s, Ar–H). MS: (35 eV, electron spray)  $m/z$  366.1 (M + 1, 100%), 367.1 (M + 2, 28%). Anal. Calcd. for C<sub>22</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: C: 61.62, H: 4.23, N: 6.53. Found: C: 61.45, H: 4.20, N: 6.42.

#### 4.1.22. 1-(4-Methoxyphenyl)-3-(4-methoxyphenyl)pyrazino[1,2-*a*]benzimidazole (**3h**)

Yield: 74%. m.p. 210–211 °C. IR(KBr) $\nu_{\text{maks}}$ ( $\text{cm}^{-1}$ ): 1626–1505 (C=N and C=C), 1280, 1216 (C–O–Ar),  $^1\text{H NMR}$ (500 MHz)(DMSO- $d_6$ )  $\delta$  (ppm): 3.83 (3H, s, OCH<sub>3</sub>), 3.88 (3H, s, OCH<sub>3</sub>), 7.09 (2H, J: 8.80 Hz, Ar–H), 7.16 (2H, d, J: 8.98 Hz, Ar–H), 7.51 (1H, t, J: 7.45 Hz and 7.61 Hz, Ar–H), 7.61 (1H, d, J: 8.06 Hz and 7.23 Hz, Ar–H), 8.01 (1H, d, J: 8.24 Hz, Ar–H), 8.18 (2H, d, J: 8.76 Hz, Ar–H), 8.50 (1H, d, J: 8.99 Hz), 9.03 (2H, d, J: 8.15 Hz, Ar–H), 9.48 (1H, s, Ar–H). Anal. Calcd. for C<sub>24</sub>H<sub>19</sub>N<sub>3</sub>O: C: 78.88, H: 5.24, N: 11.50. Found: C: 79.02, H: 5.28, N: 11.64.

#### 4.1.23. 1-(4-Methoxyphenyl)-3-(4-fluorophenyl)pyrazino[1,2-*a*]benzimidazole (**3i**)

Yield: 65%. m.p. 211–213 °C. IR(KBr) $\nu_{\text{maks}}$ ( $\text{cm}^{-1}$ ): 1615–1509 (C=N ve C=C), 1288, 1218 (C–O–Ar),  $^1\text{H NMR}$ (500 MHz)(DMSO- $d_6$ )  $\delta$  (ppm): 3.90 (3H, s, OCH<sub>3</sub>), 7.22 (2H, J: 9.91 Hz, Ar–H), 7.43 (2H, t, J: 8.84 Hz, Ar–H), 7.56–7.59 (1H, m, Ar–H), 7.66–7.68 (1H, m, Ar–H), 8.06 (1H, d, J: 9.00 Hz, Ar–H), 8.33–8.37 (2H, m, Ar–H), 8.57 (1H, d, J: 8.26 Hz), 9.07 (2H, d, J: 8.96 Hz, Ar–H), 9.68 (1H, s, Ar–H). Anal. Calcd. for C<sub>23</sub>H<sub>16</sub>FN<sub>3</sub>O<sub>2</sub>: C: 74.78, H: 4.37, N: 11.38. Found: C: 74.34, H: 4.22, N: 11.05.

#### 4.1.24. 1-(4-Methoxyphenyl)-3-(4-chlorophenyl)pyrazino[1,2-*a*]benzimidazole (**3j**)

Yield: 79%. m.p. 226–227 °C. IR(KBr) $\nu_{\text{maks}}$ ( $\text{cm}^{-1}$ ): 1609–1490 (C=N and C=C), 1278, 1222 (C–O–Ar),  $^1\text{H NMR}$ (500 MHz)(DMSO- $d_6$ )  $\delta$  (ppm): 3.88 (3H, s, OCH<sub>3</sub>), 7.16 (2H, J: 8.90 Hz, Ar–H), 7.53 (1H, t, J: 7.36 Hz and 7.80 Hz, Ar–H), 7.59 (2H, d, J: 8.55 Hz, Ar–H), 7.62 (1H, t, J: 7.49 Hz and 6.63 Hz, Ar–H), 8.02 (1H, d, J: 8.24 Hz, Ar–H), 8.27 (2H, d, J: 8.55 Hz, Ar–H), 8.50 (1H, d, J: 8.23 Hz, Ar–H), 9.01 (2H, d, J: 8.88 Hz, Ar–H), 9.63 (1H, s, Ar–H). Anal. Calcd. for C<sub>23</sub>H<sub>16</sub>ClN<sub>3</sub>O: C: 71.60, H: 4.18, N: 10.89. Found: C: 71.65, H: 4.26, N: 11.00.

#### 4.1.25. 1-(4-Chlorophenyl)-3-phenylpyrazino[1,2-*a*]benzimidazole (**3k**)

Yield: 83%. m.p. 251–252 °C. IR(KBr) $\nu_{\text{maks}}$ ( $\text{cm}^{-1}$ ): 1600–1498 (C=N and C=C), 1280, 1221 (C–O–Ar),  $^1\text{H NMR}$ (500 MHz)(DMSO- $d_6$ )  $\delta$  (ppm): 2.41 (3H, s, CH<sub>3</sub>), 7.33 (2H, J: 8.98 Hz, Ar–H), 7.54 (1H, t, J: 7.25 Hz and 7.88 Hz, Ar–H), 7.63 (1H, t, J: 7.31 and 7.98 Hz, Ar–H), 7.68 (1H, d, J: 9.63 Hz, Ar–H), 8.02 (1H, d, J: 8.10 Hz, Ar–H), 8.14 (2H, d, J: 8.54 Hz, Ar–H), 8.25 (1H, d, J: 8.54 Hz, Ar–H), 9.05 (2H, d, J: 8.64 Hz, Ar–H), 9.62 (1H, s, Ar–H). Anal. Calcd. for C<sub>22</sub>H<sub>14</sub>ClN<sub>3</sub>: C: 74.26, H: 3.97, N: 11.81. Found: C: 74.45, H: 4.20, N: 11.52.

#### 4.1.26. 1-(4-Chlorophenyl)-3-(4-methylphenyl)pyrazino[1,2-*a*]benzimidazole (**3l**)

Yield: 85%. m.p. 256–257 °C. IR(KBr) $\nu_{\text{maks}}$ ( $\text{cm}^{-1}$ ): 1616–1500 (C=N and C=C),  $^1\text{H NMR}$ (500 MHz)(DMSO- $d_6$ )  $\delta$  (ppm): 2.41 (3H, s, CH<sub>3</sub>), 7.29 (2H, J: 8.16 Hz, Ar–H), 7.57–6.60 (1H, m, Ar–H), 7.66–7.69 (1H, m, Ar–H), 7.74 (2H, d, J: 8.66 Hz, Ar–H), 8.07 (1H, d, J: 8.26 Hz, Ar–H), 8.21 (2H, d, J: 8.16 Hz, Ar–H), 8.61 (1H, d, J: 8.28 Hz, Ar–H), 9.11 (2H, d, J: 8.67 Hz, Ar–H), 9.73 (1H, s, Ar–H). Anal. Calcd. for C<sub>23</sub>H<sub>13</sub>ClN<sub>3</sub>: C: 74.69, H: 4.36, N: 11.36. Found: C: 74.73, H: 4.23, N: 11.20.

#### 4.1.27. 1-(4-Chlorophenyl)-3-(4-methoxyphenyl)pyrazino[1,2-*a*]benzimidazole (**3m**)

Yield: 70%. m.p. 220–223 °C. IR(KBr) $\nu_{\text{maks}}$ ( $\text{cm}^{-1}$ ): 1622–1510 (C=N and C=C), 1285, 1220 (C–O–Ar),  $^1\text{H NMR}$ (500 MHz)(DMSO- $d_6$ )  $\delta$  (ppm): 3.86 (3H, s, OCH<sub>3</sub>), 7.56–6.61 (1H, m, Ar–H), 7.66–7.69 (1H, m, Ar–H), 7.75 (2H, d, J: 8.67 Hz, Ar–H), 8.07 (1H, d, J: 8.32 Hz, Ar–H), 8.25 (2H, d, J: 8.79 Hz, Ar–H), 8.60 (1H, d, J: 8.26 Hz, Ar–H), 9.11 (2H, d, J: 8.68 Hz, Ar–H), 9.70 (1H, s, Ar–H). MS: (35 eV, electron spray)  $m/z$  386.1 (M + 1, 100%), 387.1 (M + 2, 25%), 388.0 (M + 3, 36%). Anal. Calcd. for C<sub>23</sub>H<sub>16</sub>ClN<sub>3</sub>O: C: 71.60, H: 4.18, N: 10.89. Found: C: 72.00, H: 3.90, N: 10.50.

#### 4.1.28. 1-(4-Chlorophenyl)-3-(4-fluorophenyl)pyrazino[1,2-*a*]benzimidazole (**3n**)

Yield: 83%. m.p. 255–257 °C. IR(KBr) $\nu_{\text{maks}}$ ( $\text{cm}^{-1}$ ): 1612–1490 (C=N and C=C),  $^1\text{H NMR}$ (500 MHz)(DMSO- $d_6$ )  $\delta$  (ppm): 7.32 (2H, t, J: 7.95 Hz, Ar–H), 7.50 (1H, t, J: Ar–H), 7.58–7.62 (3H, m, Ar–H), 7.97 (1H, d, J: 8.22 Hz, Ar–H), 8.21 (2H, dd, J: 8.67 Hz and 5.52 Hz, Ar–H), 8.45 (1H, d, J: 8.22 Hz, Ar–H), 8.97 (2H, d, J: 8.65 Hz), 9.57 (1H, s, Ar–H). Anal. Calcd. for C<sub>22</sub>H<sub>13</sub>ClFN<sub>3</sub>: C: 70.69, H: 3.51, N: 11.24. Found: C: 70.60, H: 3.68, N: 11.02.

#### 4.1.29. 1-(4-Chlorophenyl)-3-(4-chlorophenyl)pyrazino[1,2-a]benzimidazole (**30**)

Yield: 86%. m.p. 248–250 °C. IR(KBr) $\nu_{\text{maks}}$ ( $\text{cm}^{-1}$ ): 1628–1510 (C=N and C=C),  $^1\text{H NMR}$ (500 MHz)(DMSO- $d_6$ )  $\delta$  (ppm): 7.56–6.60 (1H, m, Ar–H), 7.63 (2H, d, J: 8.57 Hz, Ar–H), 7.65–7.70 (1H, m, Ar–H), 7.72 (2H, d, J: 8.67 Hz, Ar–H), 8.06 (1H, d, J: 8.30 Hz, Ar–H), 8.31 (2H, d, J: 8.58 Hz, Ar–H), 8.56 (1H, d, J: 8.26 Hz, Ar–H), 9.07 (2H, d, J: 8.66 Hz, Ar–H), 9.79 (1H, s, Ar–H). Anal. Calcd. for  $\text{C}_{22}\text{H}_{13}\text{Cl}_2\text{N}_3$ : C: 67.71, H: 3.36, N: 10.77. Found: C: 68.00, H: 3.67, N: 10.55.

#### 4.2. Anticancer activity tests

The cytotoxic and/or growth inhibitory effects of the compounds were evaluated in vitro against approximately sixty human tumour cell lines derived from nine neoplastic diseases namely; Leukemia (L, 4 or 6 cell lines), Non-Small Cell Lung Cancer (NSCLC, 9 cell lines), Colon Cancer (CC, 7 cell lines), Central Nervous System Cancer (CNSC, 6 cell lines), Melanoma (M, 8 or 9 cell lines), Ovarian Cancer (OC, 6 or 7 cell lines), Renal Cancer (RC, 8 cell lines), Prostate Cancer (PC, 2 cell lines), Breast Cancer (BC, 6 or 8 cell lines). 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 60 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 [21–23].

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