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Short communication

Synthesis of some novel benzofuran-2-yl(4,5-dihyro-3,5-substituted diphenylpyrazol-1-yl) methanones and studies on the antiproliferative effects and reversal of multidrug resistance of human MDR1-gene transfected mouse lymphoma cells *in vitro*

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ABSTRACT

A new series of benzofuran-2-yl(4,5-diydro-3,5-substituted diphenylpyrazol-1-yl) methanone derivatives **8a**–**x** by the reaction of the benzofuran-2-carbohydrazides **7** with various chalcone derivatives **3a**–**x** using microwave irradiation has been described. The effect of synthesized compounds **8a**–**v** was studied against human cancer cell lines for their antiproliferative activity and reversal of multidrug resistance on human MDR1-gene transfected mouse lymphoma cells. Among the 24 compounds, the **8c** and **8h** showed good antiproliferative activity **8b**, **8f** and **8k** were exhibited good MDR reversal activity. The main significance of the process is easy workup process, short reaction time and high yield of the new compounds for biological interest. However, the studies on genetically modified multidrug resistant cancer cells are costly and time consuming.

1. Introduction

Nowadays, one of the main problem related with treatment of human neoplastic diseases is the phenomenon of multidrug resistance (MDR) to the many anticancer agents used in chemotherapy [1,2], by increasing drug efflux, acquire cross-resistance to many structurally and functionally unrelated anticancer agents, which therefore never achieve effective intracellular concentrations [3,4]. The multidrug resistance of cancer cells is often associated with the over expression of P-glycoprotein (P-gp). Recent studies showed that tumor cells expressing MDR-associated protein (MRP), lung resistant protein (LRP) and mutation of DNA topoisomerase II are likely to be MDR [4,5]. Although several mechanisms have been reported, MDR results mainly from the over expression of ATP-binding cassette (ABC) transporters, such as, ABCB1 (P-glycoprotein, P-gp), ABCC1–7 (multidrug resistant related protein 1–7, MRP1–7) and ABCG2 (breast cancer resistance protein, BCRP), which pump out a enormous number of chemically dissimilar anticancer agents. P-gp is viewed as a therapeutic target for re-sensitizing multidrug resistant cancer cells to anticancer agents because it is considered to be more clinically significant than the other transporters.

Numerous structurally different drugs used in treating a variety of pathological conditions having MDR-reversing properties such as verapamil [6], trifluoperazine [7], and quinine [8]. Moreover, benzofurans and pyrazoles [9,10] are very interesting heterocycles, which are ubiquitous in nature and show a broad range of biological activities. Recently, the anticancer and antiviral activities of the natural cyclopenta[b]benzofurans [11] and 4,5-dihydropyrazole [12] have been reported, the same as for a variety of benzofuran derivatives. For example, 1-[(benzofuran-2-yl)phenylmethyl] imidazoles (I) had a potent, reversible, non-selective aromatase-inhibitory effect [13] and 2-{4-[(benzofuran-2-yl)carbonyl] piprazin-1-yl}-3-propylpyridine (II) exhibited good anti-HIV activity [14]. Moreover, various synthetic methodologies have been described for the synthesis of benzofuran bearing pyrazole derivatives for biological interest [15,16].

In the fight against cancer, recognition of novel potent, less toxic and selective anticancer agents remains one of the most vital health problems. During the course of our ongoing interest on syntheses of

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Table 1
Synthesis of some novel benzofuran-2-yl(4,5-dihyro-3,5-substituted diphenylpyrazol-1-yl) methanones.

Entry	R	R^1	Time (min)	Yield %
8a	H	H	12	82
8b	H	4-CH_3	14	86
8c	H	4-NO_2	10	80
8d	H	3,4-di-OCH_3	12	84
8e	H	4-F	11	82
8f	H	4-Cl	14	88
8g	H	2-Cl	12	80
8h	H	4-OCH_3	12	86
8i	4-Cl	H	11	80
8j	4-Cl	4-Cl	10	86
8k	4-Cl	4-OCH_3	14	88
8l	4-Cl	4-NO_2	11	84
8m	4-Cl	2-Cl	13	80
8n	4-Cl	3,4-di-OCH_3	12	82
8o	4-Cl	4-CH_3	14	88
8p	4-Cl	4-F	12	86
8q	4-F	H	15	82
8r	4-F	4-Cl	11	86
8s	4-F	4-OCH_3	13	84
8t	4-F	4-NO_2	10	86
8u	4-F	2-Cl	13	86
8v	4-F	3,4-di-OCH_3	12	86
8w	4-F	4-CH_3	14	88
8x	4-F	4-F	14	84

various heterocyclic molecules for biological interest, we previously reported that dihydropyridines and dihydropyrimidines are potent active against MDR reversal cell line in tumor cells [17–21]. In continuation of ongoing project, we have synthesized some novel benzofuran functionalized pyrazole derivatives using microwave irradiation and found good active against MDR reversal in tumor cells. Among them, few compounds were exhibited well antiproliferative activity.

2. Chemistry

All chalcone derivatives have been synthesized by reported procedure using substituted aldehydes and acetophenones [22]. The reaction of salisaldehyde **5** with ethyl bromoacetate **4** in the presence of base on reflux afforded ethyl benzofuran-2-carboxylate **6**. Further, the reaction of **6** with hydrazine hydrate at 0–5 °C yielded the desired benzofuran-2-carbohydrazides **7**. The reaction of **7** and **3a**–**x** in the presence of glacial acetic acid gave title molecules **8a**–**x** under microwave irradiation and the results are cited in Table 1 (Scheme 1).

3. Biological activity on multidrug resistant cancer cells

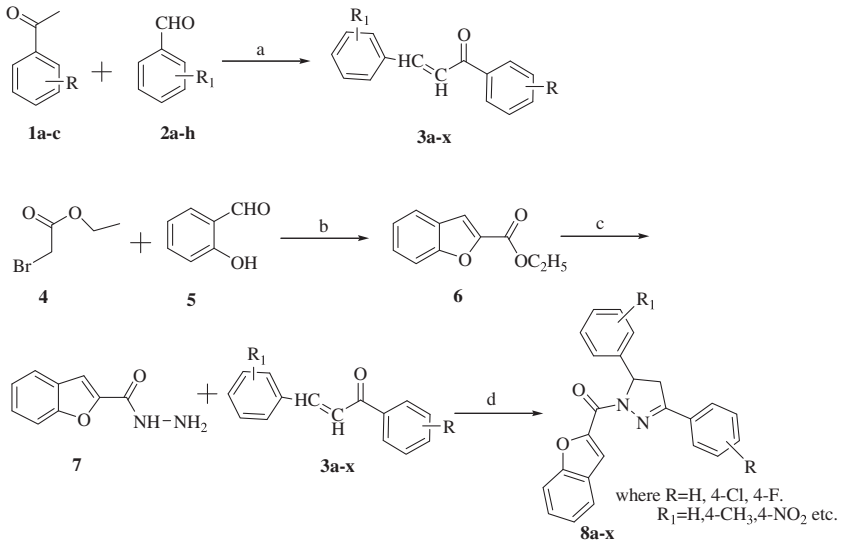
3.1. Cell cultures

L5178Y mouse T-cell lymphoma cells (ECACC cat. no. 87111908, U.S. FDA, Silver Spring, MD, USA) were transfected with pHa MDR1/A retrovirus, as described previously [23,24]. The MDR1-expressing cell line was selected by culturing the infected cells with 60 ng/ml colchicine to maintain the expression of the MDR phenotype. L5178Y (parental, PAR) mouse T-cell lymphoma cells and the human *mdr1*-transfected subline (MDR) were cultured at 37 °C in McCoy's 5A medium supplemented with 10% heat-inactivated horse serum, L-glutamine and antibiotics. The mouse lymphoma cell lines were maintained in a 5% CO_2 atmosphere at 37 °C.

A2780cis cell line (ECACC cat. no. 93112517, Salisbury, UK) has been developed by chronic exposure of the parental cisplatin-sensitive A2780 human ovary cancer cell line to increasing concentrations of cisplatin [25,26]. This cell line was cultured in RPMI 1640 medium supplemented with 10% heat-inactivated foetal bovine serum, L-glutamine and antibiotics. In order to retain resistance, cisplatin has to be added to the medium every 2–3 passages in 1 μM final concentration. The A2780cis cell line was maintained in a 5% CO_2 atmosphere at 37 °C.

3.2. Assay for antiproliferative effect

The effects of increasing concentrations of the drugs on cell growth were tested in 96-well flat-bottomed microtitre plates in one parallel. The compounds were diluted in two-steps from a starting concentration of 50 μg/ml in a final volume of 150 μl, and DMSO was used as a control. A total of 6×10^3 cells in 50 μl of medium were then added to each well, with the exception of the medium control wells. The culture plates were further incubated at 37 °C for 72 h, at the end of which 15 μl of MTT solution (thiazolyl blue solved in PBS to a final concentration of 5 mg/ml) were added



Scheme 1. Microwave assisted synthesis of substituted benzofuran bearing pyrazoline derivatives (a) NaOH, EtOH, stirred at rt, (b) K_2CO_3, DMF, reflux 1.5 h, (c) $NH_2NH_2.H_2O$, 0–5 °C, (d) glacial acetic acid, MW.

to each well. After further incubation at 37 °C for 4 h, 100 μl of sodium dodecyl sulphate (SDS) solution (10%) were measured into each well and the plates were further incubated at 37 °C overnight. The cell growth was determined by measuring the optical density (OD) at 550 nm (ref. 630 nm) with a Multiscan EX ELISA reader (Thermo Labsystems, Cheshire, WA, USA). Inhibition of cell growth was determined as a percentage according to the formula:

$$100 - \left[\frac{\text{OD treated cells} - \text{OD medium control}}{\text{OD cell control} - \text{OD medium control}} \times 100\right]$$

The result described in Table 2 indicates that compounds **8c** and **8h** exhibit good antiproliferative activity, when compounds **8a**, **8d**–**8g**, **8j** and **8n** show moderate antiproliferative activity.

3.3. Assay for reversal of MDR in tumor cells

The cells were adjusted to a density of 2×10^6 cells/ml, resuspended in serum-free McCoy's 5A medium and distributed in 0.5 ml aliquots into Eppendorf centrifuge tubes. The tested compounds were added at different final concentrations (2.0 and 20 μg/ml), and the samples were incubated for 10 min at room temperature. Indicator rhodamine 123 (R123) (Sigma–Aldrich Kft, Budapest, Hungary) was added to each sample to a final concentration of 10 μg/ml and the cells were incubated for a further 20 min at 37 °C, washed twice and resuspended in 0.5 ml phosphate-buffered saline (PBS) for analysis. The fluorescence of the cell population was measured with a FACStar Plus flow cytometer (Beckton, Dickinson and Company, Franklin Lakes, NJ, USA). Verapamil (EGIS Pharmaceuticals PLC, Budapest, Hungary) was used as a positive control in the R123 exclusion experiments at final concentration of 22 μM. The percentage mean fluorescence intensity was calculated for the treated MDR/PAR and A2780cis cell lines as compared with the untreated cells. Fluorescent activity ratio (FAR) was calculated *via* the following equation, on the basis of the measured fluorescence values:

$$\text{FAR} = \frac{\text{MDR treated/MDR control}}{\text{parental treated/parental control}}$$

The results presented are obtained from a representative flow cytometric experiment in which 1×10^5 individual cells of the population were evaluated for the amount of R123 retained are first presented by the FACS Star Plus flow cytometer as histograms and the data were converted to FAR units that define fluorescence intensity, standard deviation, peak channel in the total and in the gated populations (Table 3).

Table 2
Antiproliferative effect in IC_{50} value of newly synthesized compounds.

Compound	IC_{50} (μg/ml)	Compound	IC_{50} (μg/ml)
8a	7.58	**8l**	34.125
8b	16.602	**8m**	44.79
8c	4.866	**8n**	6.29
8d	6.888	**8q**	**11.765**
8e	9.936	**8r**	**>50**
8f	5.134	**8s**	22.997
8g	6.219	**8t**	>50
8h	4.569	**8u**	45.193
8i	13.632	**8v**	>50
8j	8.496	**8w**	>50
8k	5.743	**8x**	>50

The IC_{50} values below 10 μg/ml (**8a**, **8c**–**h**, **8j**, **8k** and **8n**) were considered as very effective, "good" while the compounds with IC_{50} value between 10 and 50 μg/ml were classified as "moderately active" (**8b**, **8i**, **8l**, **8m**, **8q**, **8s** and **8u**). The other tested compounds had no antiproliferative activity at the highest applied concentration, 50 μg/ml.

Table 3
Multidrug resistance reversal activity of compounds **8a**–**x** on *MDR1*-transfected mouse lymphoma (MDR) cell line by measuring the amount the fluorescent dye R123.

Compound	Final cc.	FAR	Compound	Final cc.	FAR
8a	20 μg/ml	18.8	**8l**	20 μg/ml	12.61
8b	20 μg/ml	7.59	**8m**	20 μg/ml	6.02
8c	20 μg/ml	15.18	**8n**	20 μg/ml	5.87
8d	20 μg/ml	29.9	**8q**	20 μg/ml	15.82
8e	20 μg/ml	20.06	**8r**	20 μg/ml	6.96
8f	20 μg/ml	8.34	**8s**	20 μg/ml	8.72
8g	20 μg/ml	16.1	**8t**	20 μg/ml	12.58
8h	20 μg/ml	26.77	**8u**	20 μg/ml	16.94
8i	20 μg/ml	6.77	**8v**	20 μg/ml	16.22
8j	20 μg/ml	2.9	**8w**	20 μg/ml	10.52
8k	20 μg/ml	5.85	**8x**	20 μg/ml	14.56

FAR*: Fluorescence Activity Ratio.
The results are from one representative flow cytometric experiment in which 1×10^4 individual cells were investigated.

4. Results and discussion

Three groups of the compounds were studied for antiproliferative effects according to the IC_{50} values measured on the human *MDR1*-gene transfected mouse lymphoma cell line: strong antiproliferative effect $0 < IC_{50} < 10$ μg/ml (10 compounds), moderate antiproliferative effect $10 < IC_{50} < 50$ μg/ml (7 compounds) and no antiproliferative effect where $IC_{50} > 50$ μg/ml was found and the results are cited in Table 2. Half of the compounds (12 compounds: **8a**, **8c**–**e**, **8g**, **8h**, **8l**, **8q**, **8t**–**8x**) had significant MDR inhibitory effect on MDR cells in the flow cytometric experiment measuring the accumulation of R123 fluorescent dye with FAR values above 10 when applying the compounds in 20 μg/ml final concentration. Other half of the compounds showed only moderate effect on reversal of multidrug resistance with FAR values below 10.

The antiproliferative effect of the compounds was different. The lowest IC_{50} value was found 4.569 μg/ml (**8h**) while some compounds were ineffective even at the applied 50 μg/ml concentration (i.e. **8r**). However, it is difficult to evaluate the connection between chemical structures and affectivity of benzofuran methanones. At any rate some substitutions on R1 position increased the antiproliferative activity, because 4 (**8d**, **8h**, **8n** and **9k**) of the best 10 compounds contained the functional group, however further investigations are required to clarify the effects of several functional groups at different positions.

The possible correlation between the FAR values and the chemical structure of the compounds need some QSAR evaluation related to rational drug design. The majority of compounds were found good resistance modifiers according to their higher FAR values in comparison with the positive control verapamil. Interestingly, the nontoxic compound **8h** with the lowest IC_{50} value (4.569 μg/ml) was found to be the second most active one as MDR reversal agent with FAR value of 26.77 in the flow cytometric experiment.

5. Experimental procedures

5.1. Materials and methods

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and visualized by iodine and UV. All the compounds were purified using Flash chromatography. IR spectra were recorded in Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC–MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was recorded on a Bruker Ac 400 MHz spectrometer in DMSO-d_6/$CDCl_3$ solution. Elemental analysis of all the

synthesized compounds was carried out using Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

5.2. Preparation of ethyl benzofuran-2-carboxylate **6**

To the mixture of salisaldehyde (0.01 mole) and DMF (30 ml), were added ethyl bromoacetate (0.01 mole) and K_2CO_3 (0.03 mole). The reaction mixture was refluxed for 1.5 h at 100 °C on oil bath. After completion of the reaction, reaction mixture was poured into crushed ice. Then product was extracted using ethyl acetate (50 ml × 3), the combined organic layer was washed using brine solution (20 ml × 2). The organic layer was dried using anhydrous sodium sulphate and the solvent evaporated under reduced pressure to acquire the product in a viscous liquid form. Yield – 77%, bp – 276 °C.

5.3. Preparation of benzofuran-2-carbohydrazides **7**

The mixture of hydrazine hydrazide (15 ml) and ethyl benzofuran-2-carboxylate (0.01 mole) was stirred at 0–5 °C for 30 min. The reaction is being monitored by TLC (hexane:ethyl acetate 4:6). Further, the reaction mixture was stirred at room temperature to give benzofuran-2-carbohydrazide as a white colored shining product. mp: 190–194 °C.

5.4. General procedure of synthesis of benzofuran-2-yl (4,5-dihydro-3,5-substituted diphenylpyrazol-1-yl) methanones **8a–x**

To a solution of benzofuran hydrazide (0.01 mole) and glacial acetic acid (10 ml), were added substituted chalcones (0.01 mole). The reaction mixture was heated in microwave synthesizer for appropriate time (Table 1). The reaction is being monitored by TLC using hexane:ethyl acetate (4:6). After completion of the reaction, the mixture was poured into crushed ice. Filtered out the separated solid product and dried under reduced pressure. Finally, it was purified by flash chromatography using hexane–ethyl acetate as eluents.

5.4.1. (Benzofuran-2-yl)(4,5-dihydro-3,5-diphenylpyrazol-1-yl) methanone (**8a**)

mp – 210–212, IR (KBr, cm^{-1}): 3059, 2920, 1691, 1641, 1545, 1186, 1109, 962; ^{1}H NMR (400 MHz) δ (ppm): 3.25 (1H, m), 3.88 (1H, m), 5.84 (1H, m), 7.31 (6H, m), 7.43 (1H, m), 7.49 (3H, m), 7.59 (1H, m), 7.84 (3H, m), 8.12 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 20.8, 40.0, 40.6, 41.4, 61.3, 111.0, 111.3, 112.0, 115.0, 122.8, 123.1, 123.8, 125.6, 127.1, 127.2, 127.8, 128.9, 130.8, 130.9, 141.3, 146.9, 154.7, 156.1, 156.4; MS $m/z = 366$ (M^+); Anal. Calcd. for $C_{24}H_{18}N_2O_2$: C, 78.67; H, 4.95; N, 7.65; O, 8.73. Found: C, 78.64; H, 4.92; N, 7.61; O, 8.70%.

5.4.2. (Benzofuran-2-yl)(4,5-dihydro-3-phenyl-5-p-tolylpyrazol-1-yl)methanone (**8b**)

mp – 180–182, IR (KBr, cm^{-1}): 3059, 2941, 1695, 1637, 1546, 1184, 1109, 960; ^{1}H NMR (400 MHz) δ (ppm): 2.28 (3H, s), 3.26 (1H, m), 3.82 (1H, m), 5.83 (1H, m), 7.12 (2H, d, $J = 8.0$ Hz), 7.21 (2H, d, $J = 8.0$ Hz), 7.30 (1H, t), 7.42 (1H, t), 7.51 (3H, m), 7.59 (1H, d, $J = 8.0$ Hz), 7.76 (1H, d, $J = 8.0$ Hz), 7.84 (2H, m), 8.03 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 21.1, 41.3, 61.1, 112.3, 114.8, 122.8, 123.3, 125.7, 126.9, 127.6, 128.9, 129.6, 130.7, 131.2, 137.5, 138.3, 147.1, 154.9, 156.1, 156.3; MS $m/z = 380$ (M^+); Anal. Calcd. for $C_{25}H_{20}N_2O_2$: C, 78.93; H, 5.30; N, 7.36; O, 8.41. Found: C, 78.91; H, 5.26; N, 7.30; O, 8.40%.

5.4.3. (Benzofuran-2-yl)(4,5-dihydro-5-(4-nitrophenyl)-3-phenylpyrazol-1-yl)methanone (**8c**)

mp – 170–172, IR (KBr, cm^{-1}): 3032, 2935, 1697, 1600, 1518, 1184, 1109, 964; ^{1}H NMR (400 MHz) δ (ppm): 3.29 (1H, m), 3.80 (1H, m), 5.86 (1H, m), 7.16 (2H, d, $J = 8.0$ Hz), 7.28 (2H, d, $J = 8.0$ Hz), 7.41 (1H, t), 7.44 (1H, t), 7.64 (3H, m), 7.69 (1H, d, $J = 8.0$ Hz), 7.80 (1H, d, $J = 8.0$ Hz), 7.88 (2H, m), 8.13 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 59.6, 109.0, 111.6, 120.6, 120.9, 121.0, 123.3, 124.7, 127.9, 128.7, 128.9, 129.2, 129.5, 130.5, 130.9, 131.1, 134.0, 146.4, 149.6, 150.0, 151.8, 158.4, 165.0; MS $m/z = 411$ (M^+); Anal. Calcd. for $C_{24}H_{17}N_3O_4$: C, 70.07; H, 4.16; N, 10.21; O, 15.56. Found: C, 70.04; H, 4.12; N, 10.20; O, 15.51%.

5.4.4. (Benzofuran-2-yl)(4,5-dihydro-5-(3,4-dimethoxyphenyl)-3-phenylpyrazol-1-yl)methanone (**8d**)

mp – 150–154, IR (KBr, cm^{-1}): 3044, 2922, 1690, 1638, 1543, 1180, 1112, 962; ^{1}H NMR (400 MHz) δ (ppm): 3.22 (1H, m), 3.66 (1H, m), 3.70(6H, s), 5.83 (1H, m), 6.52 (1H, m), 6.61 (2H, m), 7.19 (2H, m), 7.30 (3H, m), 7.49 (2H, m), 7.60 (2H, m), 7.59 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 56.2, 56.6, 59.9, 109.0, 111.6, 112.0, 115.1, 120.3, 121.0, 123.3, 124.7, 128.6, 128.9, 129.2, 129.5, 130.5, 131.1, 134.0, 136.8, 147.8, 149.6, 150.0, 151.8, 158.4, 165.0; MS $m/z = 426$ (M^+); Anal. Calcd. for $C_{26}H_{22}N_2O_4$: C, 73.23; H, 5.20; N, 6.57; O, 15.01. Found: C, 73.22; H, 5.20; N, 6.51; O, 15.00%.

5.4.5. (Benzofuran-2-yl)(5-(4-fluorophenyl)-4,5-dihydro-3-phenylpyrazol-1-yl)methanone (**8e**)

mp – 220–224, IR (KBr, cm^{-1}): 3055, 2922, 1694, 1646, 1540, 1188, 1114, 966, 1018; ^{1}H NMR (400 MHz) δ (ppm): 3.28 (1H, m), 3.86 (1H, m), 5.80 (1H, m), 7.19 (2H, d, $J = 8.0$ Hz), 7.28 (2H, d, $J = 8.0$ Hz), 7.36 (1H, t), 7.39 (1H, t), 7.50 (3H, m), 7.55 (1H, d, $J = 8.0$ Hz), 7.72 (1H, d, $J = 8.0$ Hz), 7.89 (2H, m), 8.12 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 59.6, 109.0, 111.6, 115.3, 115.5, 121.0, 123.3, 124.7, 128.4, 128.6, 128.7, 128.9, 129.2, 129.6, 130.5, 131.1, 134.0, 139.1, 150.0, 151.8, 158.4, 160.9, 165.0; MS $m/z = 384$ (M^+), 386 (M^{+2}); Anal. Calcd. for $C_{24}H_{17}FN_2O_2$: C, 74.99; H, 4.46; N, 7.29; O, 8.32. Found: C, 74.96; H, 4.42; N, 7.22; O, 8.31%.

5.4.6. (Benzofuran-2-yl)(5-(4-chlorophenyl)-4,5-dihydro-3-phenylpyrazol-1-yl)methanone (**8f**)

mp – 240–242, IR (KBr, cm^{-1}): 3062, 2926, 1688, 1641, 1547, 1182, 1104, 966, 743; ^{1}H NMR (400 MHz) δ (ppm): 3.21 (1H, m), 3.81 (1H, m), 5.88 (1H, m), 7.13 (2H, d, $J = 8.0$ Hz), 7.26 (2H, d, $J = 8.0$ Hz), 7.33 (1H, t), 7.35 (1H, t), 7.56 (3H, m), 7.58 (1H, d, $J = 8.0$ Hz), 7.82 (1H, d, $J = 8.0$ Hz), 7.88 (2H, m), 8.11 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 59.6, 109.0, 111.6, 121.0, 123.3, 124.7, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.2, 129.4, 130.5, 131.1, 132.3, 134.0, 141.6, 150.0, 151.8, 158.4, 165.0; MS $m/z = 401$ (M^+), 403 (M^{+2}); Anal. Calcd. for $C_{24}H_{17}ClN_2O_2$: C, 71.91; H, 4.27; N, 6.99; O, 7.98. Found: C, 71.88; H, 4.24; N, 6.92; O, 7.91%.

5.4.7. (Benzofuran-2-yl)(5-(2-chlorophenyl)-4,5-dihydro-3-phenylpyrazol-1-yl)methanone (**8g**)

mp – 178–182, IR (KBr, cm^{-1}): 3044, 2930, 1694, 1643, 1548, 1183, 1110, 961, 745; ^{1}H NMR (400 MHz) δ (ppm): 3.25 (1H, m), 3.88 (1H, m), 5.84 (1H, m), 7.09 (3H, m), 7.22 (3H, m), 7.30 (3H, m), 7.42 (1H, m), 7.49 (1H, m), 7.60 (2H, m), 8.02 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.4, 50.5, 109.0, 111.6, 121.0, 123.3, 124.7, 126.7, 128.2, 128.4, 128.7, 128.8, 128.9, 129.1, 129.2, 130.5, 131.1, 132.3, 134.0, 143.5, 150.0, 151.8, 158.4, 165.0; MS $m/z = 401$ (M^+), 403 (M^{+2}); Anal. Calcd. for $C_{24}H_{17}ClN_2O_2$: C, 71.91; H, 4.27; N, 6.99; O, 7.98. Found: C, 71.90; H, 4.22; N, 6.92; O, 7.96%.

5.4.8. (Benzofuran-2-yl)(4,5-dihydro-5-(4-methoxyphenyl)-3-phenylpyrazol-1-yl)methanone (**8h**)

mp – 168–170, IR (KBr, cm^{-1}): 3052, 2928, 1692, 1648, 1539, 1184, 1112, 961; ^{1}H NMR (400 MHz) δ (ppm): 2.26 (3H, s), 3.22 (1H, m), 3.81 (1H, m), 5.85 (1H, m), 7.15 (2H, d, $J = 8.0$ Hz), 7.23 (2H, d, $J = 8.0$ Hz), 7.35 (1H, t), 7.42 (1H, t), 7.52 (3H, m), 7.56 (1H, d, $J = 8.0$ Hz), 7.76 (1H, d, $J = 8.0$ Hz), 7.86 (2H, m), 8.06 (1H, s); ^{13}C

NMR ($CDCl_3$) δ: 39.9, 55.9, 59.6, 109.0, 111.6, 114.1, 114.3, 121.0, 123.3, 124.7, 128.0, 128.3, 128.4, 128.9, 129.2, 129.6, 130.5, 131.1, 134.0, 135.8, 150.0, 151.8, 158.4, 158.7, 165.0; MS $m/z = 396$ (M^+); Anal. Calcd. for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07; O, 12.11. Found: C, 75.71; H, 5.02; N, 7.01; O, 12.10%.

*5.4.9. (Benzofuran-2-yl)(3-(4-chlorophenyl)-4,5-dihydro-5-phenylpyrazol-1-yl)methanone (**8i**)*

mp – 154–156, IR (KBr, cm^{-1}): 3064, 2962, 1695, 1641, 1548, 1186, 1114, 964, 756; ^1H NMR (400 MHz) δ (ppm): 3.21 (1H, m), 3.96 (1H, m), 5.84 (1H, m), 7.29 (3H, m), 7.35 (3H, m), 7.46 (1H, m), 7.52 (2H, d, $J = 8$ Hz), 7.60 (1H, d, $J = 8$ Hz), 7.86 (1H, d, $J = 8$ Hz), 7.90 (2H, d, $J = 8$ Hz), 8.08 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 59.6, 109.0, 111.6, 121.0, 123.3, 124.7, 126.8, 127.0, 127.5, 128.3, 128.6, 129.0, 129.4, 130.5, 130.6, 130.8, 132.1, 136.6, 143.5, 150.0, 151.8, 158.4, 165.0; MS $m/z = 401$ (M^+), 403 (M^{+2}); Anal. Calcd. for $C_{24}H_{17}ClN_2O_2$: C, 71.91; H, 4.27; N, 6.99; O, 7.98. Found: C, 71.87; H, 4.24; N, 6.96; O, 7.97%.

*5.4.10. (3,5-bis(4-chlorophenyl)-4,5-dihydropyrazol-1-yl) (Benzofuran-2-yl)methanone (**8j**)*

mp – 176–178, IR (KBr, cm^{-1}): 3061, 2924, 1691, 1643, 1550, 1180, 1116, 963, 744; ^1H NMR (400 MHz) δ (ppm): 3.21 (1H, m), 3.96 (1H, m), 5.84 (1H, m), 7.06 (2H, d, $J = 8$ Hz), 7.19 (2H, m), 7.22 (2H, d, $J = 8$ Hz), 7.30 (2H, d, $J = 8$ Hz), 7.42 (1H, d, $J = 8$ Hz), 7.49 (1H, d, $J = 8$ Hz), 7.60 (2H, d, $J = 8$ Hz), 8.08 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 59.6, 109.0, 111.6, 121.0, 123.3, 124.7, 128.4, 128.5, 128.7, 128.9, 129.0, 129.7, 130.1, 130.4, 130.6, 132.1, 132.3, 136.6, 141.6, 150.0, 151.8, 158.4, 165.0; MS $m/z = 435$ (M^+), 437 (M^{+2}); Anal. Calcd. for $C_{24}H_{16}Cl_2N_2O_2$: C, 66.22; H, 3.70; N, 6.44; O, 7.35. Found: C, 66.21; H, 3.66; N, 6.44; O, 7.31%.

*5.4.11. (Benzofuran-2-yl)(3-(4-chlorophenyl)-4,5-dihydro-5-(4-methoxyphenyl)pyrazol-1-yl)methanone (**8k**)*

mp – 188–190, IR (KBr, cm^{-1}): 3052, 2921, 1691, 1646, 1547, 1181, 1109, 968, 748; ^1H NMR (400 MHz) δ (ppm): 2.26 (3H, s), 3.24 (1H, m), 3.98 (1H, m), 5.81 (1H, m), 7.01 (2H, d, $J = 8$ Hz), 7.14 (2H, m), 7.23 (2H, d, $J = 8$ Hz), 7.32 (2H, d, $J = 8$ Hz), 7.44 (1H, d, $J = 8$ Hz), 7.48 (1H, d, $J = 8$ Hz), 7.62 (2H, d, $J = 8$ Hz), 8.06 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 55.9, 59.6, 109.0, 111.6, 114.1, 114.4, 121.0, 123.3, 124.7, 128.0, 128.6, 129.0, 129.4, 130.5, 130.6, 130.7, 132.1, 135.8, 136.6, 150.0, 151.8, 158.4, 158.7, 165.0; MS $m/z = 431$ (M^+), 433 (M^{+2}); Anal. Calcd. for $C_{25}H_{19}ClN_2O_3$: C, 69.69; H, 4.44; N, 6.50; O, 11.14. Found: C, 69.65; H, 4.46; N, 6.44; O, 11.12%.

*5.4.12. (Benzofuran-2-yl)(3-(4-chlorophenyl)-4,5-dihydro-5-(4-nitrophenyl)pyrazol-1-yl)methanone (**8l**)*

mp – 192–194, IR (KBr, cm^{-1}): 3050, 2930, 1688, 1640, 1546, 1181, 1115, 963, 745; ^1H NMR (400 MHz) δ (ppm): 3.25 (1H, m), 3.94 (1H, m), 5.81 (1H, m), 7.02 (2H, d, $J = 8$ Hz), 7.14 (2H, m), 7.26 (2H, d, $J = 8$ Hz), 7.34 (2H, d, $J = 8$ Hz), 7.41 (1H, d, $J = 8$ Hz), 7.45 (1H, d, $J = 8$ Hz), 7.61 (2H, d, $J = 8$ Hz), 8.12 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 59.6, 109.0, 111.6, 120.5, 120.9, 121.0, 123.3, 124.7, 127.3, 127.9, 129.0, 129.2, 130.5, 130.6, 130.8, 132.1, 136.6, 146.4, 149.6, 150.0, 151.8, 158.4, 165.0; MS $m/z = 446$ (M^+), 448 (M^{+2}); Anal. Calcd. for $C_{24}H_{16}ClN_3O_4$: C, 64.65; H, 3.62; N, 9.42; O, 14.35. Found: C, 64.62; H, 3.60; N, 9.40; O, 14.31%.

*5.4.13. (Benzofuran-2-yl)(5-(2-chlorophenyl)-3-(4-chlorophenyl)-4,5-dihydropyrazol-1-yl)methanone (**8m**)*

mp – 160–162, IR (KBr, cm^{-1}): 3064, 2926, 1696, 1641, 1540, 1186, 1109, 957, 748; ^1H NMR (400 MHz) δ (ppm): 3.21 (1H, m), 3.96 (1H, m), 5.84 (1H, m), 7.09 (3H, m), 7.22 (3H, m), 7.42 (1H, d, $J = 8$ Hz), 7.49 (1H, d, $J = 8$ Hz), 7.52 (2H, d, $J = 8$ Hz), 7.90 (2H, d, $J = 8$ Hz), 8.12 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.4, 50.5, 109.0, 111.6, 121.0, 123.3, 124.7, 126.7, 128.2, 128.4, 128.7, 129.0, 129.5, 130.4, 130.6, 130.7, 132.1, 132.3, 136.6, 143.5, 150.0, 151.8, 158.4, 165.0; MS $m/z = 435$ (M^+), 437 (M^{+2}); Anal. Calcd. for $C_{24}H_{16}Cl_2N_2O_2$: C, 66.22; H, 3.70; N, 6.44; O, 7.35. Found: C, 66.20; H, 3.71; N, 6.43; O, 7.30%.

*5.4.14. (Benzofuran-2-yl)(3-(4-chlorophenyl)-4,5-dihydro-5-(3,4-dimethoxyphenyl)pyrazol-1-yl)methanone (**8n**)*

mp – 188–190, IR (KBr, cm^{-1}): 3063, 2928, 1694, 1638, 1541, 1182, 1109, 958, 742; ^1H NMR (400 MHz) δ (ppm): 3.21 (1H, m), 3.92 (1H, m), 3.98 (6H, s), 5.84 (1H, m), 6.61 (3H,m), 7.19 (2H, m), 7.42 (1H, d, $J = 8.0$ Hz), 7.49 (1H, d, $J = 8.0$ Hz), 7.54 (2H, d, $J = 8.0$ Hz), 7.94 (2H, d, $J = 8$ Hz), 8.06 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 56.2, 56.5, 59.9, 109.0, 111.6, 112.0, 115.1, 120.3, 121.0, 123.3, 124.7, 129.0, 129.1, 130.5, 130.6, 130.7, 132.1, 136.6, 136.8, 147.8, 149.6, 150.0, 151.8, 158.4, 165.0; MS $m/z = 461$ (M^+), 463 (M^{+2}); Anal. Calcd. for $C_{26}H_{21}ClN_2O_4$: C, 67.75; H, 4.59; N, 6.08; O, 13.89. Found: C, 67.71; H, 4.55; N, 6.09; O, 13.80%.

*5.4.15. (Benzofuran-2-yl)(3-(4-chlorophenyl)-4,5-dihydro-5-p-tolylpyrazol-1-yl)methanone (**8o**)*

mp – 178–182, IR (KBr, cm^{-1}): 3061, 2925, 1696, 1648, 1541, 1180, 1111, 967, 750; ^1H NMR (400 MHz) δ (ppm): 2.29 (3H, s), 3.28 (1H, m), 3.96 (1H, m), 5.86 (1H, m), 7.11 (2H, d, $J = 8$ Hz), 7.16 (2H, m), 7.27 (2H, d, $J = 8$ Hz), 7.30 (2H, d, $J = 8$ Hz), 7.47 (1H, d, $J = 8$ Hz), 7.50 (1H, d, $J = 8$ Hz), 7.66 (2H, d, $J = 8$ Hz), 8.12 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 23.3, 24.3, 39.9, 59.6, 109.0, 111.6, 121.0, 124.7, 126.3, 126.9, 128.5, 128.9, 129.0, 129.4, 130.5, 130.6, 130.8, 132.1, 136.4, 136.6, 140.5, 150.0, 151.8, 158.4, 165.0; MS $m/z = 415$ (M^+), 417 (M^{+2}); Anal. Calcd. for $C_{25}H_{19}ClN_2O_2$: C, 72.37; H, 4.62; N, 6.75; O, 7.71. Found: C, 72.32; H, 4.60; N, 6.70; O, 7.70%.

*5.4.16. (Benzofuran-2-yl)(3-(4-chlorophenyl)-5-(4-fluorophenyl)-4,5-dihydropyrazol-1-yl)methanone (**8p**)*

mp – 220–222, IR (KBr, cm^{-1}): 3048, 2927, 1695, 1650, 1541, 1190, 1115, 968, 746, 1020; ^1H NMR (400 MHz) δ (ppm): 3.24 (1H, m), 3.92 (1H, m), 5.81 (1H, m), 7.08 (2H, d, $J = 8$ Hz), 7.17 (2H, m), 7.26 (2H, d, $J = 8$ Hz), 7.34 (2H, d, $J = 8$ Hz), 7.40 (1H, d, $J = 8$ Hz), 7.48 (1H, d, $J = 8$ Hz), 7.64 (2H, d, $J = 8$ Hz), 8.04 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 59.6, 109.0, 111.6, 115.3, 115.6, 121.0, 123.3, 124.7, 128.6, 128.8, 129.0, 129.3, 130.5, 130.6, 130.8, 132.1, 136.6, 139.1, 150.0, 151.8, 158.4, 160.9, 165.0; MS $m/z = 419$ (M^+), 421 (M^{+2}); Anal. Calcd. for $C_{24}H_{16}ClFN_2O_2$: C, 68.82; H, 3.85; N, 6.69; O, 7.64. Found: C, 68.80; H, 3.81; N, 6.62; O, 7.61%.

*5.4.17. (Benzofuran-2-yl)(3-(4-fluorophenyl)-4,5-dihydro-5-phenylpyrazol-1-yl)methanone (**8q**)*

mp – 244–246, IR (KBr, cm^{-1}): 3051, 2927, 1694, 1648, 1536, 1186, 1109, 955, 1018; ^1H NMR (400 MHz) δ (ppm): 3.20 (1H, m), 3.87 (1H, m), 5.80 (1H, m), 7.27 (8H, m), 7.38 (1H, t), 7.50 (1H, d), 7.75 (1H, d, $J = 8$), 7.84 (2H, q), 7.97 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 59.6, 109.0, 111.6, 115.6, 115.7, 121.0, 123.3, 124.7, 126.8, 127.0, 127.4, 128.2, 128.6, 129.6, 130.5, 130.7, 130.8, 143.5, 150.0, 151.8, 158.4, 165.0, 165.2; MS $m/z = 384$ (M^+), 386 (M^{+2}); Anal. Calcd. for $C_{24}H_{17}FN_2O_2$: C, 74.99; H, 4.46; N, 7.29; O, 8.32. Found: C, 74.96; H, 4.40; N, 7.25; O, 8.30%.

*5.4.18. (Benzofuran-2-yl)(5-(4-chlorophenyl)-3-(4-fluorophenyl)-4,5-dihydropyrazol-1-yl)methanone (**8r**)*

mp – 210–212, IR (KBr, cm^{-1}): 3036, 2922, 1686, 1643, 1548, 1182, 1112, 954, 740, 1020; ^1H NMR (400 MHz) δ (ppm): 3.26 (1H, m), 3.96 (1H, m), 5.85 (1H, m), 7.35 (7H, m), 7.46 (1H, m), 7.57 (1H, d, $J = 8$ Hz), 7.82 (1H, m), 7.92 (2H, m), 8.04 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 59.6, 109.0, 111.6, 115.4, 115.6, 121.0, 123.3, 124.7, 128.4, 128.5, 128.7, 128.8, 129.6, 130.3, 130.5, 130.8, 132.3, 141.6, 150.0,

151.8, 158.4, 165.0, 165.2; MS $m/z = 419$ (M^+), 421(M^{+2}); Anal. Calcd. for $C_{24}H_{16}ClFN_2O_2$: C, 68.82; H, 3.85; N, 6.69; O, 7.64. Found: C, 68.80; H, 3.81; N, 6.65; O, 7.60%.

*5.4.19. (Benzofuran-2-yl)(3-(4-fluorophenyl)-4,5-dihydro-5-(4-methoxyphenyl)pyrazol-1-yl)methanone (**8s**)*

mp – 220–222, IR (KBr, cm^{-1}): 3050, 2918, 1696, 1644, 1546, 1196, 1115, 964, 1020; ^1H NMR (400 MHz) δ (ppm): 2.22 (3H, s), 3.29 (1H, m), 3.93 (1H, m), 5.87 (1H, m), 7.06 (2H, d, $J = 8$ Hz), 7.15 (2H, m), 7.29 (2H, d, $J = 8$ Hz), 7.36 (2H, d, $J = 8$ Hz), 7.47 (1H, d, $J = 8$ Hz), 7.43 (1H, d, $J = 8$ Hz), 7.66 (2H, d, $J = 8$ Hz), 8.12 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 55.9, 59.6, 109.0, 111.6, 114.1, 114.5, 115.6, 115.8, 121.0, 123.3, 124.7, 128.0, 128.6, 129.6, 130.5, 130.6, 130.8, 135.8, 150.0, 151.8, 158.4, 158.7, 165.0, 165.2; MS $m/z = 414$ (M^+), 416 (M^{+2}); Anal. Calcd. for $C_{25}H_{19}FN_2O_3$: C, 72.45; H, 4.62; N, 6.76; O, 11.58. Found: C, 72.42; H, 4.60; N, 6.70; O, 11.51%.

*5.4.20. (Benzofuran-2-yl)(3-(4-fluorophenyl)-4,5-dihydro-5-(4-nitrophenyl)pyrazol-1-yl)methanone (**8t**)*

mp – 240–244, IR (KBr, cm^{-1}): 3063, 2921, 1694, 1641, 1547, 1190, 1114, 964, 1028; ^1H NMR (400 MHz) δ (ppm): 3.28 (1H, m), 3.91 (1H, m), 5.87 (1H, m), 7.05 (2H, d, $J = 8$ Hz), 7.18 (2H, m), 7.20 (2H, d, $J = 8$ Hz), 7.31 (2H, d, $J = 8$ Hz), 7.47 (1H, d, $J = 8$ Hz), 7.48 (1H, d, $J = 8$ Hz), 7.64 (2H, d, $J = 8$ Hz), 8.02 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 59.6, 109.0, 111.6, 115.5, 115.6, 120.3, 120.9, 121.0, 123.3, 124.7, 127.5, 127.9, 129.6, 130.2, 130.5, 130.8, 146.4, 149.6, 150.0, 151.8, 158.4, 165.0, 165.2; MS $m/z = 429$ (M^+), 431 (M^{+2}); Anal. Calcd. for $C_{24}H_{16}FN_3O_4$: C, 67.13; H, 3.76; N, 9.79; O, 14.90. Found: C, 67.10; H, 3.71; N, 9.77; O, 14.88%.

*5.4.21. (Benzofuran-2-yl)(5-(2-chlorophenyl)-3-(4-fluorophenyl)-4,5-dihydropyrazol-1-yl)methanone (**8u**)*

mp – 176–178, IR (KBr, cm^{-1}): 3048, 2926, 1697, 1641, 1541, 1188, 1112, 960, 744, 1022; ^1H NMR (400 MHz) δ (ppm): 3.20 (1H, m), 3.93 (1H, m), 5.82 (1H, m), 7.02 (3H, m), 7.26 (3H, m), 7.41 (1H, d, $J = 8$ Hz), 7.45 (1H, d, $J = 8$ *Hz*), 7.57 (2H, d, $J = 8$ Hz), 7.94 (2H, d, $J = 8$ Hz), 8.06 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.4, 50.5, 109.0, 111.6, 115.4, 115.6, 121.0, 123.3, 124.7, 126.7, 128.2, 128.4, 128.7, 129.6, 130.5, 130.7, 130.8, 132.3, 143.5, 150.0, 151.8, 158.4, 165.0, 165.2; MS $m/z = 419$ (M^+), 421 (M^{+2}); Anal. Calcd. for $C_{24}H_{16}ClFN_2O_2$: C, 68.82; H, 3.85; N, 6.69; O, 7.64. Found: C, 68.80; H, 3.81; N, 6.66; O, 7.61%.

*5.4.22. (Benzofuran-2-yl)(3-(4-fluorophenyl)-4,5-dihydro-5-(3,4-dimethoxyphenyl)pyrazol-1-yl)methanone (**8v**)*

mp – 164–166, IR (KBr, cm^{-1}): 3038, 2938, 1690, 1655, 1544, 1184, 1112, 960, 1021; ^1H NMR (400 MHz) δ (ppm): 3.29 (1H, m), 3.96 (1H, m), 3.88 (6H, s), 5.89 (1H, m), 6.70 (3H,m), 7.29 (2H, m), 7.48 (1H, d, $J = 8.0$ Hz), 7.55 (1H, d, $J = 8.0$ Hz), 7.59 (2H, d, $J = 8.0$ Hz), 7.90 (2H, d, $J = 8$ Hz), 8.08 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 56.2, 56.5, 59.9, 109.0, 111.6, 112.0, 115.1, 115.6, 115.7, 120.3, 121.0, 123.3, 124.7, 129.6, 130.5, 130.6, 130.8, 136.8, 147.8, 149.6, 150.0, 151.8, 158.4, 165.0, 165.2; MS $m/z = 444$ (M^+), 446 (M^{+2}); Anal. Calcd. for $C_{26}H_{21}FN_2O_4$: C, 70.26; H, 4.76; N, 6.30; O, 14.40. Found: C, 70.22; H, 4.70; N, 6.31; O, 14.38%.

*5.4.23. (Benzofuran-2-yl)(3-(4-fluorophenyl)-4,5-dihydro-5-p-tolylpyrazol-1-yl)methanone (**8w**)*

mp – 174–176, IR (KBr, cm^{-1}): 3044, 2936, 1689, 1651, 1548, 1180, 1112, 966, 1024; ^1H NMR (400 MHz) δ (ppm): 2.23 (3H, s), 3.22 (1H, m), 3.99 (1H, m), 5.80 (1H, m), 7.18 (2H, d, $J = 8$ Hz), 7.11 (2H, m), 7.21 (2H, d, $J = 8$ Hz), 7.36 (2H, d, $J = 8$ Hz), 7.49 (1H, d, $J = 8$ Hz), 7.58 (1H, d, $J = 8$ Hz), 7.68 (2H, d, $J = 8$ Hz), 8.02 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 24.3, 39.9, 59.6, 109.0, 111.6, 115.6, 120.1, 121.4, 123.3, 124.7, 126.4, 126.9, 128.6, 128.8, 129.6, 130.5, 130.7, 130.9, 136.4, 140.5, 150.0, 151.8, 158.4, 165.0, 165.2; MS $m/z = 398$ (M^+), 400 (M^{+2}); Anal. Calcd. for $C_{25}H_{19}FN_2O_2$: C, 75.36; H, 4.81; N, 7.03; O, 8.03. Found: C, 75.30; H, 4.81; N, 7.00; O, 8.01%.

*5.4.24. (3,5-bis(4-fluorophenyl)-4,5-dihydropyrazol-1-yl)(Benzofuran-2-yl)methanone (**8x**)*

mp – 184–186, IR (KBr, cm^{-1}): 3042, 2935, 1696, 1656, 1542, 1180, 1115, 966, 1022; ^1H NMR (400 MHz) δ (ppm): 3.20 (1H, m), 3.94 (1H, m), 5.87 (1H, m), 7.00 (2H, d, $J = 8$ Hz), 7.14 (2H, m), 7.28 (2H, d, $J = 8$ Hz), 7.38 (2H, d, $J = 8$ Hz), 7.46 (1H, d, $J = 8$ Hz), 7.49 (1H, d, $J = 8$ Hz), 7.67 (2H, d, $J = 8$ Hz), 8.05 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 39.9, 59.6, 109.0, 111.6, 115.3, 115.6, 115.8, 115.9, 121.0, 123.3, 124.7, 128.3, 128.6, 129.6, 130.5, 130.8, 130.9, 139.1, 150.0, 151.8, 158.4, 160.9, 165.0, 165.2; MS $m/z = 402$ (M^+), 404 (M^{+2}); Anal. Calcd. for $C_{24}H_{16}F_2N_2O_2$: C, 71.64; H, 4.01; N, 6.96; O, 7.95. Found: C, 71.60; H, 4.01; N, 6.92; O, 7.90%.

6. Conclusion

We have demonstrated a facile and rapid synthesis of benzofuran-2-yl(4,5-diydro-3,5-substituted diphenylpyrazol-1-yl) methanones under microwave irradiation. All the synthesized compounds were examined for antiproliferative activity and the ability to reverse multidrug resistance in human *MDR1*-gene transfected mouse lymphoma (MDR) cells *in vitro*. In our experiments the antiproliferative effects, the IC50 values of the compounds were similar, concentration however the inhibitory action on the function of over expressed ABC transporter in cancer cells were strictly dependent on the chemical structures of benzofuran methanones, resulting in increased rhodamine accumulation in cancer cell model. The compounds **8b**, **8c**, **8f**, **8h** and **8k** were found high inhibitory effect against MDR reversal activity.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.02.045.

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