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Design, Synthesis and Anticancer Activity of Novel Dihydropyrazole and Benzothiazole Conjugates.

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ABSTRACT

A series of N-(substituted benzo[d]thiazolyl)dihydropyrazolyl)acetamides conjugates have been synthesized. The structures of twenty four novel compounds were characterized by ^{1}HNMR, IR and Mass. Evaluated their anti-cancer activity in breast cancer cell lines and liver cancer cell lines. The results of MTT assay shows that among the series of compounds studied six compounds in MCF-7 cell lines and eight compounds in Hep G2 cell lines have cytotoxicity. The compound with methoxy substitution on benzothiazole ring and chloro and nitro substitutions on phenyl rings attached to pyrazole is found to be highly cytotoxic to both the cell lines studied among the series of the compound prepared.

Keywords: Dihydropyrazole, benzothiazole, anticancer activity, cytotoxicity

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INTRODUCTION

Pyrazole and benzothiazole derivatives are well established in the literature as important biologically active heterocyclic compounds. These derivatives are the subject of many research studies due to their wide spread potential biological activities such as anti-inflammatory[1], anti-microbial[2], anti-viral[3], anti-tumour[4-5], anti-convulsant[6], anti-depressant[7]. Some of 4,5-dihydro-1H-pyrazoles possess important pharmacological activities such as anti-tumor[8] and anti-inflammatory activities[9]. Few of oxime containing pyrazole derivatives exhibit regulators for apoptosis and autophagy in A549 Lung cancer cells[10]. 2-(4-Aminophenyl) benzothiazole was found to elicit pronounced inhibitory effects against certain breast cancer cell lines in vitro with an intriguing biphasic dose-response relationship [11]. Planar, hydrophobic amino phenyl benzothiazole analogues are potent agonists for the aryl hydrocarbon receptor (AhR). Substituted 4-Aminophenyl benzothiazoles were exhibits unique antitumor activities[12].

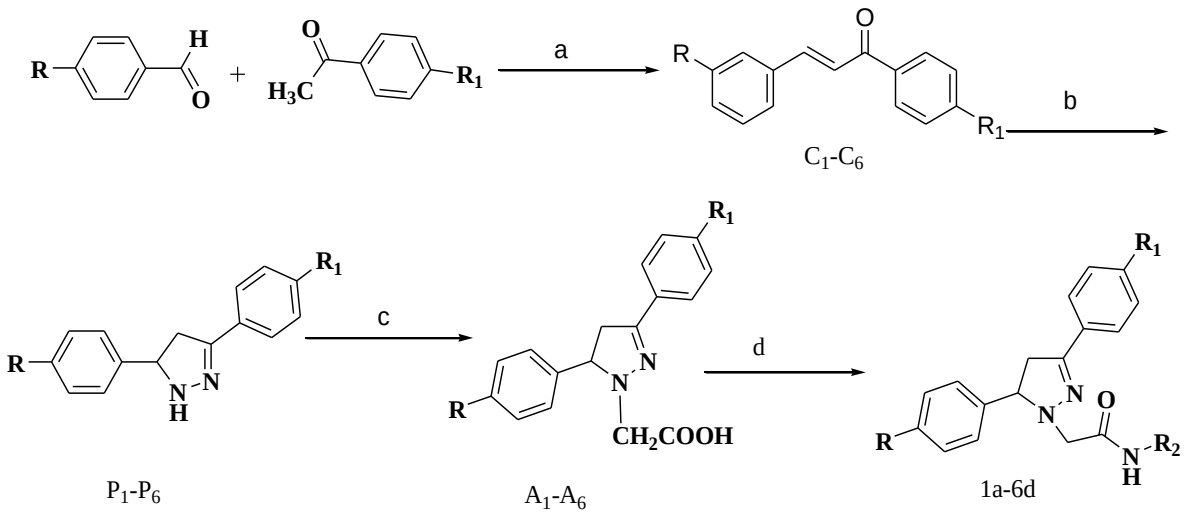
In view of the above mentioned facts, it was envisaged that these active pharmacophores, if linked together would generate novel molecular templets which are likely to exhibit interesting biological properties. In continuation of our interest in the synthesis of biologically active heterocycles, we report herein the synthesis and anti cancer activity of some new conjugates of N-(substituted benzo [d] thiazolyl) dihydropyrazolyl) acetamides.

This combination was suggested in an attempt to investigate the influence of such structure variation on the anticipated biological activities, hoping to add some synergistic biological significance to the target molecules.

RESULTS AND DISCUSSION

Chemistry

The synthetic strategies adopted for the synthesis of the target compounds are depicted in **Scheme-1**.The starting material used in the present scheme i.e., pyrazole derivatives **p_1-p_6** are prepared by treating the chalcones **C_1-C_6** with hydrazine hydrate in presence of ethanol[12-13], which on reaction with halo carboxylic acids in the presence of base yielded corresponding pyrazolyl carboxylic acids **A_1-A_6**. The compounds **1a-6d** was obtained by condensing pyrazolyl carboxylic acids **A_1-A_6** with substituted amino benzothiazoles in the presence of EDCI/DMAP. The structures of all the newly synthesized compounds were elucidated on the basis of their spectral (IR, NMR and Mass) and elemental analyses data. The synthesized compounds **1a-6d** were also assayed for their anti cancer activity.



Scheme-1

a: NaOH, EtOH, **b**: $N_2H_4.H_2O$, EtOH, reflux, **c**: Chloro acetic acid, NaOH / EtOH, reflux,
d: Substituted amino benzthiazoles, DMAP/ EDCI, dry DCM.

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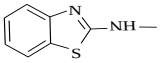
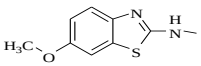
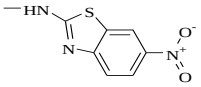
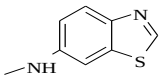
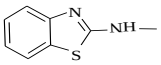
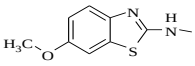
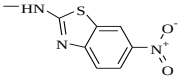
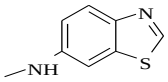
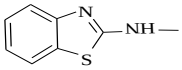
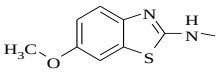
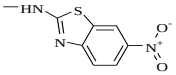
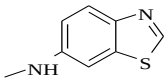
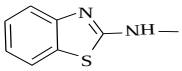
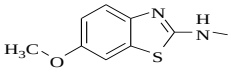
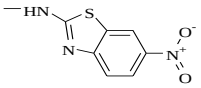
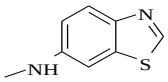
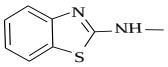
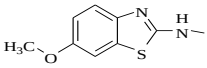
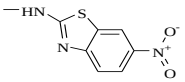
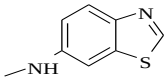
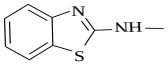
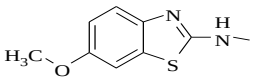
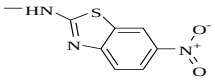
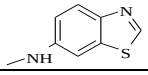
S. No	Compound	R	R_1	R_2
1	1a	-H	-H	
2	1b	-H	-H	
3	1c	-H	-H	
4	1d	-H	-H	
5	2a	-Cl	$-NO_2$	
6	2b	-Cl	$-NO_2$	
7	2c	-Cl	$-NO_2$	
8	2d	-Cl	$-NO_2$	
9	3a	$-OCH_3$	$-NO_2$	
10	3b	$-OCH_3$	$-NO_2$	
11	3c	$-OCH_3$	$-NO_2$	
12	3d	$-OCH_3$	$-NO_2$	
13	4a	-Cl	$-OCH_3$	
14	4b	-Cl	$-OCH_3$	
15	4c	-Cl	$-OCH_3$	
16	4d	-Cl	$-OCH_3$	
17	5a	$-OCH_3$	$-OCH_3$	
18	5b	$-OCH_3$	$-OCH_3$	
19	5c	$-OCH_3$	$-OCH_3$	
20	5d	$-OCH_3$	$-OCH_3$	
21	6a	$-CH_3$	$-OCH_3$	
22	6b	$-CH_3$	$-OCH_3$	
23	6c	$-CH_3$	$-OCH_3$	
24	6d	$-CH_3$	$-OCH_3$	

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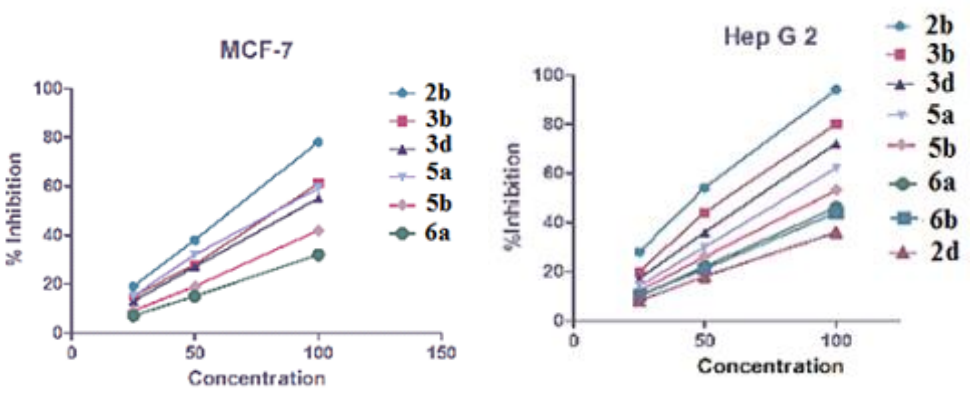
Anticancer activity:

Cytotoxicities profile from the **figures 1** and **Table 1** reveals that among the series of compounds studied only six compounds in MCF-7 cell lines and eight compounds in Hep G2 cell lines have cytotoxicity. The results also demonstrate that the compounds **(1a, 1b, 1c and 1d)** with no substitution and the compounds **(4a, 4b, 4c and 4d)** with chloro and methoxy substitutions on the phenyl rings attached to pyrazole are not showing any cytotoxicity towards both the cell lines studied. In general, the compounds **(2b, 3b, 5b, 6b)** with methoxy substitution on benzothiazole ring are showing better cytotoxicity against liver cancer cell lines among the series of the compounds except the compound **(1b)** with no substitution and the compound **(4b)** with chloro and methoxy substitution on phenyl rings attached to pyrazole.

The compound **(2b)** with methoxy substitution on benzothiazole ring and chloro and nitro substitutions on phenyl rings attached to pyrazole is found to be highly cytotoxic to both the cell lines studied among the series of the compound prepared. It is also observed from the results that may the nitro substitution on benzothiazole ring encumbering the compounds **(1c, 2c, 3c, 4c, 5c and 6c)** being cytotoxic to the cell lines studied. The results also demonstrate that in majority of the cases the compounds with 2-substituted benzothiazoles are better cytotoxic than the compounds **(1d, 2d, 4d, 5d** and **6d)** with 6-substituted benzothiazoles except the compound **3d.**



(A) **(B)**

Figure 1:- Cytotoxicities of Conjugates (2b –6b) in Hep G -2 cell lines and MCF-7cell lines using MTT assay. (A) refers to the cytoxicities of 2b, 3b, 3d, 5a, 5b and 6a in MCF 7 cell lines and (B) refers to the cytotoxicities 2b, 2d, 3b, 3d, 5a, 5b, 6a and 6b in Hep G -2 cell lines.

Table-1. IC $_{50}$ (µg/mL) values of Compounds (2b-6d)

Compound	IC_{50} values against liver cancer cell line (Hep G-2)	IC_{50} values against breast cancer cell line (MCF-7)
2b	48.35	64.67
2d	137.31	-------
3b	60.86	83.06
3d	69.72	91.07
5a	81.25	83.62
5b	94.37	118.53
6a	108.33	154.05
6b	101.25	-------
Cis-platin	33.69	21.69

CONCLUSIONS

In conclusion, we synthesized and studied the anticancer activity of a series of novel dihydropyrazole and benzothiazole conjugates. The results show that some of these compounds are showing anticancer activity against breast cancer cell lines and liver cancer cell lines. It is found that among the series of the compounds

synthesized the compound with methoxy substitution on benzothiazole ring and chloro and nitro substitutions on phenyl rings attached to pyrazole is found to be highly cytotoxic to both the cell lines were studied. Hence, it can be concluded that by the conjugation of dihydropyrazole and benzothiazole units the anticancer activity may be improved.

EXPERIMENTAL METHODS

General

Melting points were recorded in open capillary and were uncorrected. IR spectra (KBr) were obtained using a Bruker WM-4(X) spectrometer (577 model). Mass spectral data were acquired by using a commercial LCQ ion trap mass spectrometer (ThermoFinnigan, San Jose, CA, USA) equipped with an ESI source. ^{1}H NMR (300 MHz, DMSO-d_6) and ^{13}C NMR (75 MHz, DMSO-d_6) spectra were recorded on a Varian FT 300 MHz NMR Spectrometer. All the starting materials were obtained from Aldrich or Fluka used as received. The progress of the reaction was monitored by thin-layer chromatography using 0.25 mm silica gel plates. Column chromatography was performed using silica gel (Acme Synthetic Chemicals, India; finer than 200 and 60–120 mesh).

Chemical Methods

General procedure for the synthesis of substituted 4,5-dihydro-3,5-diphenyl-*1H*-pyrazoles (P_1-P_6):

To a mixture of chalcones **C_1-C_6** (10 mmol) in ethanol (20 mL) and hydrazine hydrate (10 mmol) and catalytic amount of piperidine were added and the reaction mixture was refluxed for 4-6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, the solid separated filtered washed with water and recrystallized in DMF to obtained compounds.

General procedure for the synthesis of substituted 4, 5-dihydro-3, 5-diphenyl-*1H*-pyrazolyl acetic acids (A_1-A_6):

A mixture of compounds **P_1-P_6** (9 mmol) and chloroacetic acid (9 mmol) were added to a stirring solution of NaOH (18 mmol of NaOH dissolves in 100 mL of ethanol) at such a rate that the temperature did not exceed 30 °C. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature poured into ice cold water, neutralized with hydrochloric acid, solid separated, filtered, dried and recrystallised from ethanol to obtain compounds.

General procedure for the synthesis of N-(substituted benzo[d]thiazolyl)-dihydropyrazolyl) acetamides (1a-6d):

To a mixture of compound A_1-A_6 (0.35 mmol) and substituted 2-Amino/6-amino benzothiazoles (0.35 mmol), in dry dichloromethane (10 mL), EDCI (0.35 mmol) and DMAP (0.035 mmol) were added and the reaction mixture was stirred for 16 hours at room temperature. The reaction was monitored by TLC. After completion of reaction, the solvent was evaporated under vaccuo and the residue was extracted with dichloromethane and washed with water. The organic layer was dried over anhydrous sodiumsulphate and the solvent was evaporated under vaccuo obtained crude which was purified by column chromatography using (10:90 ethyl acetate: hexane (v/v) as mobile phase to obtain the title compounds in good yields.

***N*-(benzo[d]thiazol-2-yl)-2-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)acetamide (1a):**

Yield 65%; it was obtained as light green solid, mp: 150-151 ^{o}C. IR (cm^{-1}): 1705 (C=O), 1670 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.2 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.1 [s, 2H, -HN-C$\underline{H}_2$-], 3.5 [t, 1H, Ar-C$\underline{H}$- CH_2-], 5.6 [br,1H, -N$\underline{H}$-C=O], 7.0 [m, 1H, aromatic], 7.2 [m, 2H, aromatic], 7.3 [m, 2H, aromatic], 7.4 [m, 4H, aromatic], 7.6[m, 2H, aromatic], 7.8 [m, 1H, aromatic], 8.1 [m, 2H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 41.2 (CH_2), 51.6 (CH), 56.7 (NCH_2), 122.6 (=CH), 127.5 (=CS), 127.8 (=CH), 128.4, 128.9, 129.4, 130.1, 131.4, 132.8, 136.2, 136.4, 151.2 (=CH), 154.4 (C=N), 169.4 (C=O), 179.2 (N=C-S). Mass spectrum (LCM): m/z 413 $[M+H]^+$ for

$C_{24}H_{20}N_4OS$. Elemental Analysis: Calculated : %N: 13.58, %C: 69.88, %H: 4.89, %S: 7.77. Observed : %N: 13.90, %C: 69.59, %H: 4.78, %S: 7.86.

2-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)-*N*-(6-methoxybenzothiazol-2-yl)acetamide (1b):

Yield 60%; it was obtained as blue solid, mp: 152-153 ^{o}C. IR (cm^{-1}): 1705 (C=O), 1665 (C=N), 1275 (C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.2 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.1 [s, 2H, -HN-C$\underline{H}_2$-], 3.5 [t, 1H, Ar-C$\underline{H}$- CH_2-], 3.9 [s, 3H, Ar-OC$\underline{H}_3$-], 5.6 [br,1H,-N$\underline{H}$-C=O], 7.0-7.1 [m, 4H, aromatic], 7.2 [m, 2H, aromatic], 7.3 [m, 3H, aromatic], 7.6 [m, 3H, aromatic], 8.1 [s, 1H, aromatic]. ^{13}C NMR(75 MHz,DMSO-d_6) δ/ppm: 41.2 (CH_2), 51.5 (CH), 56.4 (NCH_2), 57.2 (OCH_3), 109.2 (=CH), 112.8, 123.2, 127.7 (=CHS), 128.4 (=CH), 129.4, 130.0, 131.2, 131.4, 132.4, 134.0, 136.4, 139.0, 140.4 (=CHN), 151.8 (C=N), 169.2 (C=O), 174.6 (=CNH). Mass spectrum (LCM): m/z 442 $[M]^+$ for $C_{25}H_{22}N_4O_2S$. Elemental Analysis: Calculated : %N: 12.66, %C:67.85, %H: 5.01, %S: 7.25. Observed : %N: 12.30, %C: 67.65, %H: 5.85, %S: 7.05.

2-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)-*N*-(6-nitrobenzothiazol-2-yl) acetamide(1c):

Yield 63%; it was obtained as light yellow solid, mp: 245-247 ^{o}C. IR (cm^{-1}): 1705 (C=O), 1668 (C=N), 1370 (NO_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.2 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.1 [s, 2H, -HN-C$\underline{H}_2$-], 3.5 [t, 1H, Ar-C$\underline{H}$-CH_2-], 5.6 [br,1H,-N$\underline{H}$-C=O], 7.0-7.1 [m, 3H, aromatic], 7.2 [m, 2H, aromatic], 7.3 [m, 3H, aromatic], 7.5 [m, 2H, aromatic], 8.5 [m, 2H, aromatic], 8.7 [s, 1H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 40.2 (CH_2), 51.4 (=CH), 56.2 (CH_2), 118.2 (=CH), 120.0, 123.2, 126.4, 127.4, 128.2, 129.3, 130.2, 130.8, 132.1, 134.9, 146.2 (=CHN), 152.1 (C=N), 156.2 (C=CN), 169.9 (C=O), 175.2 (NHC=N). Mass spectrum (LCM): m/z 458$[M+H]^+$ for $C_{24}H_{19}N_5O_3S$. Elemental Analysis: Calculated : %N: 15.31, %C: 63.01, %H: 4.19, %S: 7.01. Observed : %N: 15.02, %C: 63.20, %H: 4.05, %S: 7.35.

***N*-(benzothiazol-6-yl)-2-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)acetamide (1d):**

Yield 68%; it was obtained as white solid, mp: 154-155 ^{o}C. IR (cm^{-1}): 1705 (C=O), 1665 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.1 [s, 2H, -HN-C$\underline{H}_2$-], 3.5 [t, 1H, Ar-C$\underline{H}$- CH_2-], 5.6 [br, 1H, -N$\underline{H}$-C=O], 7.0-7.1 [m, 3H, aromatic], 7.2 [m, 2H, aromatic], 7.3 [m, 3H, aromatic], 7.6[m, 2H, aromatic], 7.9 [m, 1H, aromatic], 8.2 [m, 1H, aromatic], 8.6[m, 1H, aromatic], 8.7[m, 1H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 40.2 (CH_2), 50.8 (CHN), 56.9 (NCH_2), 111.2 (=CH), 120.4, 121.8, 128.8, 129.2, 129.3, 129.9, 130.6, 130.9, 137.2, 139.3, 150.2 (=CHN), 152.3 (C=N), 158.2 (CH=N), 170.2 (C=O). Mass spectrum (LCM): m/z 412 $[M]^+$ for $C_{24}H_{20}N_4OS$. Elemental Analysis: Calculated : %N: 13.58, %C: 69.88, %H: 4.89, %S: 7.77. Observed : %N: 13.78, %C: 69.95, %H: 4.85, %S: 7.65.

***N*-(benzothiazol-2-yl)-2-(5-(4-chlorophenyl)-4,5- dihydro-3-(4-nitrophenyl) pyrazol-1-yl)acetamide (2a):**

Yield 68%; it was obtained as light green solid, mp: 180-181 ^{o}C. IR (cm^{-1}): 1705 (C=O), 1669 (C=N), 1365 (NO_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.2 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 2.5 [s, 2H, O=C-C$\underline{H}_2$-], 3.4[t, 1H, Ar-C$\underline{H}$-CH_2-], 5.5 [br,1H, -N$\underline{H}$-C=O], 7.0 [m, 2H, aromatic], 7.2 [m, 2H, aromatic], 7.6 [m, 2H, aromatic], 7.8 [m, 2H, aromatic], 8.1 [m, 1H, aromatic], 8.2 [m, 3H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6)δ/ppm: 40.6 (CH_2), 51.2 (CHN), 56.2 (NCH_2), 123.3 (=CH), 123.4, 125.9, 126.2, 126.4, 129.8, 131.4, 131.6, 134.2 (=CHCl), 137.9 (=CH), 142.2 (C=C), 150.2 (=CN), 151.2 (=CNO_2), 152.9 (=CN), 169.9 (C=O), 176.2 (-NHC=N. Mass spectrum (LCM): m/z 491 $[M]^+$ for $C_{24}H_{18}ClN_5O_3S$. Elemental Analysis: Calculated: %N: 14.24, %C: 58.59, %H: 3.69, %S: 6.52. Observed: %N: 14.55, %C: 58.40, %H: 3.75, %S: 6.82.

2-(5-(4-chlorophenyl)-4,5- dihydro-3-(4-nitrophenyl) pyrazol-1-yl)-*N*-(6-methoxybenzothia zol-2-yl) acetamide (2b):

Yield 65%; it was obtained as blue solid, mp: 210-211 ^{o}C. IR (cm^{-1}): 1710 (C=O), 1670 (C=N), 1370 (NO_2), 1275 (C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.2 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 2.5 [s, 2H, O=C-C$\underline{H}_2$-], 3.3 [t, 1H, Ar-C$\underline{H}$- CH_2-], 3.9 [s, 3H, Ar-OC$\underline{H}_3$-], 5.6 [br,1H,-N$\underline{H}$-C=O], 7.1 [m, 3H, aromatic], 7.3 [m, 2H, aromatic], 7.6 [s, 1H, aromatic], 8.0-8.1 [m, 2H, aromatic], 8.2 [m, 3H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6)δ/ppm: 41.2 (CH_2), 51.2 (CHN), 56.5 (NCH_2), 57.3 (OCH_3), 108.9 (C=C), 112.8, 123.4, 123.6, 126.9, 129.4, 130.2, 130.8, 130.9, 131.7, 133.8 (C=CCl), 139.2 (C=C), 141.0, 151.8 (C=CNO_2), 152.8 (C=N), 157.8 (C=C), 169.9 (C=O), 176.4 (NHC=N). Mass

spectrum (LCM): m/z 522 $[M+H]^+$ for $C_{25}H_{20}ClN_5O_4S$. Elemental Analysis: Calculated: %N: 13.42, %C: 57.53, %H: 3.86, %S: 6.14. Observed: %N: 13.55, %C: 57.90, %H: 3.50, %S: 6.15.

2-(5-(4-chlorophenyl)-4,5-dihydro-3-(4-nitrophenyl)pyrazol-1-yl)-*N*-(6-nitrobenzothiazol-2-yl) acetamide (2c):

Yield 70%; it was obtained as light yellow solid, mp: 230-231 ^oC. IR (cm^{-1}): 1710 (C=O), 1665 (C=N), 1365 (NO_2). ^1H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1[dd, 2H, Ph-CH-C$\underline{H_2}$-], 2.5 [s, 2H, O=C-C$\underline{H_2}$-], 3.3 [t, 1H, Ar-C$\underline{H}$-CH_2-], 5.6 [br, 1H, -N$\underline{H}$-C=O],7.1 [m, 2H, aromatic], 7.2 [m, 2H, aromatic], 7.8 [m, 2H, aromatic], 8.1 [m, 2H, aromatic], 8.5 [m, 2H, aromatic], 9 [s, 1H, aromatic].

^{13}C NMR (75 MHz, DMSO-d_6)δ/ppm: 40.7 (CH_2), 51.4 (CHN), 56.5 (NCH_2), 121.3 (C=C), 121.8, 123.4, 123.6, 126.3, 130.0, 131.2, 131.6, 134.2 (C=CCl), 141.5 (C=C), 148.2 (C=CNO_2), 151.3 (C=CNO_2), 152.6 (C=N), 169.8 (C=O), 176.5 (NHC=N). Mass spectrum (LCM): m/z 537 $[M+H]^+$ for $C_{24}H_{17}ClN_6O_5S$. Elemental Analysis: Calculated: %N: 15.65, %C: 53.68, %H: 3.19, %S: 5.97. Observed: %N: 15.88, %C: 53.75, %H: 3.23, %S: 5.91.

***N*-(benzothiazol-6-yl)-2-(5-(4-chlorophenyl)-4,5-dihydro-3-(4-nitrophenyl)pyrazol-1-yl)acetamide (2d):**

Yield 71%; it was obtained as white solid, mp: 223-224 ^oC. IR (cm^{-1}): 1705 (C=O), 1670 (C=N), 1370 (NO_2). ^1H NMR (300 MHz, DMSO-d_6) δ/ppm 2.1(dd, 2H, Ph-CH-C$\underline{H_2}$-), 2.5 (s, 2H, O=C-C$\underline{H_2}$-), 3.3 (t, 1H, Ar-C$\underline{H}$-CH_2-), 5.6 (br,1H,-N$\underline{H}$-C=O),7.0 (m, 2H, Ar-H), 7.2 (m, 2H, Ar-H), 7.8 (m, 3H, Ar-H), 8.2 (m, 3H, Ar-H), 8.5 (m, 1H, Ar-H), 9.2 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6)δ/ppm: 40.5 (CH_2), 51.3 (CHN), 56.5 (NCH_2), 112.3 (C=C), 120.5, 122.3, 123.5, 129.9, 131.3, 131.6, 134.3 (C=CCl), 136.3 (C=CS), 137.2 (C=CNH), 141.6 (C=C), 150.2 (C=CN), 151.2 ((C=CNO_2)), 152.5 (C=N), 157.2 (SC=N), 169.8 (C=O). Mass spectrum (LCM): m/z 492 $[M+H]^+$ for $C_{24}H_{18}ClN_5O_3S$. Elemental Analysis: Calculated: %N: 14.24, %C: 58.59, %H: 3.69, %S: 6.52. Observed: %N: 14.45, %C: 58.70, %H: 3.80, %S: 6.35.

***N*-(benzothiazol-2-yl)-2-(4,5-dihydro-5-(4-methoxyphenyl)-3-(4-nitrophenyl)pyrazol-1-yl)acetamide (3a):**

Yield 74%; it was obtained as light green solid, mp: 240-242 ^oC. IR (cm^{-1}): 1710(C=O), 1670 (C=N), 1370 (NO_2), 1260 (C-O-C). ^1H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.3 [dd, 2H, Ph-CH-C$\underline{H_2}$-], 3.5-3.6 [s, 2H, O=C-C$\underline{H_2}$-], 3.7[t, 1H, Ar-C$\underline{H}$- CH_2-], 3.9 [s, 3H, Ar-OC$\underline{H_3}$-], 5.4 [br,1H, -N$\underline{H}$-C=O], 6.8 [m, 2H, aromatic], 7.1 [m, 2H, aromatic], 7.5 [m, 2H, aromatic], 8.1 [m, 3H, aromatic], 8.3 [m, 3H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6)δ/ppm: 41.0 (CH_2), 51.2 (CHN), 56.3 (OCH_3), 56.5 (NCH_2), 114.6 (C=C), 115.2 , 122.3, 122.8, 123.5, 126.3, 126.8 (C=CS), 131.3 (C=C), 131.5, 132.3, 141.4, 150.2 (C=CN), 151.4 (C=CNO_2), 152.5 (C=N), 160.2 (C=CO), 169.2 (C=O), 175.8 (N=CNH). Mass spectrum (LCM): m/z 487 $[M]^+$ for $C_{25}H_{21}N_5O_4S$. Elemental Analysis: Calculated: %N: 14.36, %C: 61.59, %H: 4.34, %S: 6.58. Observed: %N: 14.65, %C: 61.35, %H: 4.60, %S: 6.40.

2-(4,5-dihydro-5-(4-methoxyphenyl)-3-(4-nitrophenyl)pyrazol-1-yl)-*N*-(6-methoxybenzothiazol-2-yl) acetamide (3b):

Yield 68%; it was obtained as blue solid, mp: 250-251 ^oC. IR (cm^{-1}): 1710 (C=O), 1665 (C=N), 1370 (NO_2), 1265 (C-O-C). ^1H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.2 [dd, 2H, Ph-CH-C$\underline{H_2}$-], 3.5-3.6 [s, 2H, O=C-C$\underline{H_2}$-], 3.7 [t, 1H, Ar-C$\underline{H}$- CH_2-], 3.9 [s, 6H, Ar-OC$\underline{H_3}$-x 2], 5.4 [br,1H,-N$\underline{H}$-C=O], 6.8 [m, 2H, aromatic], 7.1 [m, 3H, aromatic], 7.6 [s, 1H, aromatic], 8.0 [m, 2H, aromatic], 8.2 [m, 3H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6)δ/ppm: 40.2 (CH_2), 51.3 (CHN), 55.3 (CH_2N), 56.2 (OCH_3), 56.5 (OCH3), 104.8 (C=C), 115.2, 115.3, 122.4, 123.2, 126.5, 129.8, 131.2, 131.3, 141.2, 142.3 (C=CN), 151.3 (C=CNO_2), 152.3 (C=N), 157.4 (C=CO), 160.2 (C=CO), 169.8 (C=O), 175.9 (SC=N): Mass spectrum (LCM): m/z 518 $[M+H]^+$ for $C_{26}H_{23}N_5O_5S$. Elemental Analysis: Calculated: %N: 13.53, %C: 60.34, %H: 4.48, %S: 6.20. Observed: %N: 13.30, %C: 60.50, %H: 4.25, %S: 6.45.

2- (4,5-dihydro- 5-(4-methoxyphenyl)- 3-(4- nitrophenyl) pyrazol-1-yl)-*N*-(6-nitrobenzothiazol-2-yl) acetamide (3c):

Yield 65%; it was obtained as yellow solid, mp: 230-232 ^oC. IR (cm^{-1}): 1715 (C=O), 1670 (C=N), 1365 (NO_2), 1270 (C-O-C). ^1H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.2 [dd, 2H, Ph-CH-C$\underline{H_2}$-], 3.5-3.6 [s, 2H, O=C-C$\underline{H_2}$-], 3.7[t, 1H, Ar-C$\underline{H}$- CH_2-], 3.9 [s, 3H, Ar-OC$\underline{H_3}$-], 5.4 [br, 1H,-N$\underline{H}$-C=O], 6.8 [m, 2H, aromatic], 7.1 [m, 2H, aromatic], 7.8 [m, 2H, aromatic], 8.0 [m, 2H, aromatic], 8.5 [m, 2H, aromatic], 8.7[s, 1H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6)δ/ppm 40.3 (CH_2), 51.8 (CHN), 56.3 (OCH_3), 56.9 (NCH_2), 115.2 (C=C), 115.6, 119.2, 121.9, 122.3,

124.2, 126.2 (C=CS), 130.2 (C=C), 131.3, 147.2 (C=CNO_2), 151.4 (C=CNO_2), 152.2 (C=N), 156.2 (C=CN), 159.9 (C=CO), 169.9 (C=O), 175.5 (C=CNH). Mass spectrum (LCM): m/z 532 $[M]^+$ for $C_{25}H_{20}N_6O_6S$. Elemental Analysis: Calculated: %N: 15.78, %C: 56.39, %H: 3.79, %S: 6.02. Observed: %N: 15.90, %C: 56.80, %H: 3.75, %S: 6.40.

***N*- (benzothiazol-6-yl)-2-(4,5-dihydro-5-(4-methoxyphenyl)-3-(4-nitrophenyl) pyrazol-1-yl)acetamide (3d):**

Yield 73%; it was obtained as white solid, mp: 240-241 ^oC. IR (cm^{-1}): 1710 (C=O), 1670 (C=N), 1365 (NO_2), 1270 (C-O-C). ^1H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.2 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.5-3.6 [s, 2H, O=C-C$\underline{H}_2$-], 3.7 [t, 1H, Ar-C$\underline{H}$- CH_2-], 3.9 [s, 3H, Ar-OC$\underline{H}_3$-], 5.4 [br,1H,-N$\underline{H}$-C=O], 6.8 [m, 2H, aromatic], 7.1 [m, 2H, aromatic], 8.0 [m, 3H, aromatic], 8.1 [m, 2H, aromatic], 8.3 [m, 2H, aromatic], 9.3 [s, 1H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 40.1 (CH_2), 51.9 (CHN), 56.4 (CH_2N), 56.8 (OCH_3), 111.7 (C=C), 115.2, 116.2, 121.2, 122.9, 123.5, 130.3, 131.2, 131.3, 136.2 (C=CS), 137.2 (C=CNH), 141.2 (C=C), 149.8 (C=CN), 151.3 (C=CNO_2), 152.6 (C=N), 157.2 (SC=N), 160.2 (C=CO), 169.2 (C=O). Mass spectrum (LCM): m/z 487 $[M]^+$ for $C_{25}H_{21}N_5O_4S$. Elemental Analysis: Calculated: %N: 14.36, %C: 61.59, %H: 4.34, %S: 6.58. Observed: %N: 14.40, %C: 61.60, %H: 4.50, %S: 6.30.

***N*-(benzothiazol-2-yl)-2-(5-(4-chlorophenyl)-4,5-dihydro-3-(4-methoxyphenyl)pyrazol-1-yl) acetamide (4a):**

Yield 65%; it was obtained as green solid, mp: 243-244 ^oC. IR (cm^{-1}): 1715 (C=O), 1675 (C=N), 1265 (C-O-C). ^1H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.3 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.1 [s, 2H, O=C-C$\underline{H}_2$-], 3.8[t, 1H, Ar-C$\underline{H}$-CH_2-], 3.9 [s, 3H, Ar-OC$\underline{H}_3$-], 5.4 [br,1H, -N$\underline{H}$-C=O], 7.1 [m, 2H, aromatic], 7.3 [m, 2H, aromatic], 7.6 [m, 2H, aromatic], 7.9 [m, 2H, aromatic], 8.2 [m, 2H, aromatic], 8.4 [m, 2H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 40.2 (CH_2), 51.2 (CHN), 56.2 (CH_2N), 56.8 ($0CH_3$), 115.4 (C=C), 123.4, 123.6, 126.2, 127.3 (C=CCl), 129.9 (C=C), 130.2, 130.8, 131.8, 133.2, 133.8, 137.4, 149.4 (C=CN), 152.3 (C=N), 163.9 (C=CO), 169.2 (C=O), 175.5 (C=CNH). Mass spectrum (LCM): m/z 477 $[M+H]^+$ for $C_{25}H_{21}ClN_4O_2S$. Elemental Analysis: Calculated: %N: 11.75, %C: 62.95, %H: 4.44, %S: 6.72. Observed: %N: 11.90, %C: 62.80, %H: 4.85, %S: 6.45.

2-(5-(4-chlorophenyl)- 4,5-dihydro-3- (4-methoxyphenyl) pyrazol-1-yl)- *N*-(6-methoxybenzothiazol-2-yl)acetamide (4b):

Yield 66%; it was obtained as light blue solid, mp: 170-171 ^oC. IR (cm^{-1}): 1720 (C=O), 1670 (C=N), 1265 (C-O-C). ^1H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.3 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.1 [s, 2H, O=C-C$\underline{H}_2$-], 3.8[t, 1H, Ar-C$\underline{H}$-CH_2-], 3.9 [s, 6H, Ar-OC$\underline{H}_3$-x 2], 5.4 [br,1H, -N$\underline{H}$-C=O], 7.1 [m, 2H, aromatic], 7.2 [m, 3H, aromatic], 7.4 [m, 2H, aromatic], 7.9 [m, 3H, aromatic], 8.2 [m, 1H, aromatic].

^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm 40.2 (CH_2), 51.3 (CHN), 56.0 (CH_2N), 56.6 (OCH_3), 56.9 (OCH_3), 107.2 (C=C), 114.3, 115.5 (C=CO), 123.8 (C=C), 126.2 (C=CS), 127.2 (C=C), 129.4, 129.9, 130.6, 131.2, 133.2 (C=CCl), 137.2 (C=C), 142.3, 152.5 (C=N), 157.2 (C=CO), 164.0 (C=C), 169.4 (C=O), 175.4 (N=CNH). Mass spectrum (LCM): m/z 506 $[M]^+$ for $C_{26}H_{23}ClN_4O_3S$. Elemental Analysis: Calculated: %N: 11.05, %C: 61.59, %H: 4.57, %S: 6.32. Observed: %N: 11.45, %C: 61.55, %H: 4.65, %S: 6.05.

2-(5-(4-chlorophenyl)-4,5-dihydro-3- (4-methoxyphenyl) pyrazol-1-yl) -*N*- (6-nitro benzothiazol-2-yl) acetamide (4c):

Yield 70%; it was obtained as light yellow solid, mp: 165-166 ^oC. IR (cm^{-1}): 1710 (C=O), 1675 (C=N), 1370 (NO_2), 1260 (C-O-C). ^1H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.3 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.1 [s, 2H, O=C-C$\underline{H}_2$-], 3.8[t, 1H, Ar-C$\underline{H}$- CH_2-], 3.9 [s, 3H, Ar-OC$\underline{H}_3$-], 5.4 [br,1H, -N$\underline{H}$-C=O], 7.1 [m, 2H, aromatic], 7.3 [m,2H, aromatic], 7.6 [m, 2H, aromatic], 7.9 [m, 2H, aromatic], 8.2 [m, 2H, aromatic], 8.7 [s, 1H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 40.2 (CH_2), 51.3 (CHN), 56.2 (CH_2N), 56.3 (OCH_3), 115.2 (C=C), 117.4, 121.0, 123.5, 126.5 (C=CS), 127.4, 129.7, 129.9, 130.5, 131.5, 133.2 (C=CCl), 137.5 (C=C), 146.2 (C=CNO_2), 156.3 (C=CN), 163.8 (C=CO), 169.8 (C=O), 175.2 (N=CNH). Mass spectrum (LCM): m/z 521 $[M]^+$ for $C_{25}H_{20}ClN_5O_4S$,. Elemental Analysis: Calculated: %N: 13.42, %C: 57.53, %H: 3.86, %S: 6.14. Observed: %N: 13.25, %C: 57.79, %H: 3.60, %S: 6.50.

_N_-(benzothiazol-6-yl)-2-(5-(4-chlorophenyl)-4,5-dihydro-3-(4-methoxyphenyl)pyrazol-1-yl) acetamide (4d):

Yield 68%; it was obtained as white solid, mp: 155-156 ^{o}C. IR (cm^{-1}): 1715 (C=O), 1670 (C=N), 1275 (C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.3 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.1 [s, 2H, O=C-C$\underline{H}_2$-], 3.8[t, 1H, Ar-C$\underline{H}$-CH_2-], 3.9 [s, 3H, Ar-OC$\underline{H}_3$-], 5.4 [br, 1H, -N$\underline{H}$-C=O], 7.1 [m, 2H, aromatic], 7.2 [m, 2H, aromatic], 7.3 [m, 2H, aromatic], 7.4 [m, 2H, aromatic], 7.6 [m, 1H, aromatic], 7.8 [m, 1H, aromatic], 8.1 [m, 1H, aromatic], 8.4 [s, 1H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 40.5 (CH_2), 51.5 (CHN), 56.0 (CH_2N), 56.8 (OCH_3), 111.2 (C=C), 115.4, 120.4, 123.2, 127.2, 129.7, 130.5, 130.7, 131.3, 133.5 (C=CCl), 137.2 (C=CS), 137.3 (C=CNH), 149.9 (C=CN), 156.2 (N=CS), 162.9 (C=CO), 169.9 (C=O). Mass spectrum (LCM): m/z 477 $[M+H]^+$for $C_{25}H_{21}ClN_4O_2S$]. Elemental Analysis: Calculated : %N: 11.75, %C: 62.95, %H: 4.44, %S: 6.72. Observed : %N: 11.85, %C:62.50, %H:4.65, %S: 6.45.

_N_-(benzothiazol-2-yl)-2-(4,5-dihydro-3,5-bis(4-methoxyphenyl)pyrazol-1-yl)acetamide (5a):

Yield 69%; it was obtained as light green solid, mp: 157-158 ^{o}C. IR (cm^{-1}): 1710 (C=O), 1675 (C=N), 1265 (C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.3 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.1 [s, 2H, O=C-C$\underline{H}_2$-], 3.8[t, 1H, Ar-C$\underline{H}$-CH_2-], 3.9 [s, 3H, Ar-OC$\underline{H}_3$-], 5.4 [br, 1H, -N$\underline{H}$-C=O], 7.1 [m, 2H, aromatic],7.2 [m, 2H, aromatic],7.3 [m, 2H, aromatic],7.4 [m, 2H, aromatic],7.6 [m, 1H, aromatic],7.8 [m, 1H, aromatic],8.1 [m, 1H, aromatic],8.4 [s, 1H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 40.5 (CH_2), 51.2 (CHN), 56.0 (CH_2N), 56.4 (OCH_3), 56.8 (OCH_3), 115.3 (C=C), 115.4, 123.2, 125.4 (C=CS), 127.5 (C=C), 128.8, 129.2, 130.8, 131.0, 131.5, 150.2(C=CN), 152.5 (C=N), 160.2 (C=CO), 163.4 (C=CO), 169.8 (C=O), 175.8 (N=CNH). Mass spectrum (LCM): m/z 511 $[M+K]^+$ for $C_{26}H_{24}N_4O_3S$. Elemental Analysis: Calculated: %N: 11.86, %C: 66.08, %H: 5.12, %S: 6.79. Observed: %N: 11.80, %C: 66.20, %H: 5.05, %S: 6.95.

2-(4,5-dihydro-3,5-bis (4-methoxyphenyl)pyrazol-1-yl)-_N_-(6-methoxybenzothiazol-2-yl) acetamide (5b):

Yield 70%; it was obtained as blue solid, mp: 149-150 ^{o}C. IR (cm^{-1}): 1720 (C=O), 1670 (C=N), 1260 (C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.3 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.2-3.3 [s, 2H, O=C-C$\underline{H}_2$-], 3.7[t, 1H, Ar-C$\underline{H}$-CH_2-], 3.8-3.9 [s, 9H, Ar-OC$\underline{H}_3$-x 3], 5.3-5.4 [br,1H, -N$\underline{H}$-C=O], 6.8 [m, 4H, aromatic], 7.1 [m, 3H, aromatic], 7.3[m, 3H, aromatic], 8.1 [m, 1H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 40.2 (CH_2), 51.4 (CHN), 56.2 (OCH_3), 56.4 (OCH_3), 56.9 (OCH_3), 57.2 (CH_2N), 105.2 (C=C), 114.3, 115.3, 115.6, 115.8, 123.2, 126.3 (C=CS), 127.3, 130.4, 131.2, 131.9, 152.7 (C=N), 157.8 (C=CO), 160.2 (OCH_3), 163.0 (C=CO), 169.4 (C=O), 175.8 (N=CNH). Mass spectrum (LCM): m/z 502 $[M]^+$ for $C_{27}H_{26}N_4O_4S$. Elemental Analysis: Calculated: %N: 11.15, %C: 64.52, %H: 5.21, %S: 6.38. Observed: %N: 11.40, %C: 64.35, %H: 5.25, %S: 6.50.

2-(4,5-dihydro-3,5-bis (4-methoxyphenyl)pyrazol-1-yl)-_N_-(6-nitrobenzothiazol-2-yl) acetamide (5c):

Yield:71%; it was obtained as yellow solid, mp: 230-231 ^{o}C. IR (cm^{-1}): 1715 (C=O), 1670 (C=N), 1365 (NO_2), 1260 (C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.3 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.2-3.3 [s, 2H, O=C-C$\underline{H}_2$-], 3.7[t, 1H, Ar-C$\underline{H}$- CH_2-], 3.8-3.9 [s, 6H, Ar-OC$\underline{H}_3$-x 2], 5.2-5.4 [br,1H, -N$\underline{H}$-C=O], 6.7-6.8 [m, 4H, aromatic], 7.1 [m, 2H, aromatic], 7.3 [m, 2H, aromatic], 8.4 [m, 2H, aromatic], 9.1 [s, 1H, aromatic].

^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 40.1 (CH_2), 51.3 (CHN), 56.0 (CH_2N), 56.2 (OCH_3), 56.3 (OCH_3), 115.2 (C=C), 115.7, 118.9, 121.8, 123.5, 126.2 (C=CS), 127.2 (C=C), 129.9, 131.8, 146.7 (C=CNO_2), 152.3 (N=C), 156.7 (C=CN), 160.2 (C=CO), 163.2 (C=CO), 168.3 (C=O), 175.2 (N=CNH). Mass spectrum (LCM): m/z 518 $[M+H]^+$ for $C_{26}H_{23}N_5O_5S$. Elemental Analysis: Calculated: %N: 13.53, %C: 60.34, %H: 4.48, %S: 6.20. Observed: %N: 13.55, %C: 60.50, %H: 4.35, %S: 6.45.

_N_-(benzothiazol-6-yl)-2-(4,5-dihydro-3,5-bis(4-methoxyphenyl)pyrazol-1-yl)acetamide (5d):

Yield 74%; it was obtained as white solid, mp: 163-164 ^{o}C. IR (cm^{-1}): 1720 (C=O), 1675 (C=N), 1260 (C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.1-2.3 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 3.2-3.3 [s, 2H, O=C-C$\underline{H}_2$-], 3.7[t, 1H, Ar-C$\underline{H}$-CH_2-], 3.8-3.9 [s, 6H, Ar-OC$\underline{H}_3$-x 2], 5.2-5.4 [br,1H, -N$\underline{H}$-C=O], 6.7-6.8 [m, 4H, aromatic], 7.1 [m, 2H, aromatic], 7.3[m, 2H, aromatic], 7.8[m, 1H, aromatic], 8.3 [m, 1H, aromatic], 8.6 [m, 1H, aromatic], 9.1 [s, 1H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 40.3 (CH_2), 51.6 (CHN), 56.2 (OCH_3), 56.4 (OCH_3), 111.2 (C=C), 115.2, 115.5, 120.8, 123.0, 127.3, 129.8 (C=C), 132.8, 136.2 (C=CS), 137.2 (C=CNH), 149.9 (C=CN), 152.2 (C=N), 156.5 (N=CS), 160.2 (C=CO), 163.4 (C=CO), 169.8 (C=O). Mass spectrum (LCM): m/z 472 $[M]^+$ for $C_{26}H_{24}N_4O_3S$.

Elemental Analysis: Calculated: %N: 11.86, %C: 66.08, %H: 5.12, %S: 6.79. Observed: %N: 11.85, %C: 66.20, %H: 5.75, %S: 6.15.

_N_-(benzothiazol-2-yl)-2-(4,5-dihydro-3-(4-methoxyphenyl)-5-p-tolylpyrazol-1-yl)acetamide (6a):

Yield 72%; it was obtained as green solid, mp: 164-165 ^{o}C. IR (cm^{-1}): 1715 (C=O), 1670 (C=N), 1265 (C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.2-2.3 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 2.4 [s, 3H, Ar-C$\underline{H}_3$], 3.4 [s, 2H, O=C-C$\underline{H}_2$-], 3.5[t, 1H, Ar-C$\underline{H}$- CH_2-], 3.7-3.9 [s, 3H, Ar-OC$\underline{H}_3$-], 5.3 [br,1H, -N$\underline{H}$-C=O], 6.8-7.0 [m, 4H, aromatic], 7.0-7.2 [m, 2H, aromatic], 7.5-7.7 [m, 4H, aromatic], 8.1-8.2 [m, 2H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 25.8 (CH_3), 40.8 (CH_2), 51.3 (CHN), 56.3 (OCH_3), 116.2 (C=C), 122.8, 122.9, 125.3 (C=CS), 126.0 (C=C), 126.3, 127.2, 129.2, 131.5, 131.9, 136.8, 137.8, 150.2 (C=CN), 152.7 (C=N), 163.8 (C=CO), 169.5 (C=O), 175.2 (N=CNH). Mass spectrum (LCM): m/z 457 $[M+H]^+$ for $C_{26}H_{24}N_4O_2S$. Elemental Analysis: Calculated: %N: 12.27, %C: 68.40, %H: 5.30, %S: 7.02. Observed: %N: 12.15, %C: 68.35, %H: 5.45, %S: 7.25.

2-(4,5-dihydro-3-(4-methoxyphenyl)-5-p-tolylpyrazol-1-yl)-_N_-(6-methoxybenzothiazol-2-yl) acetamide (6b):

Yield 63%; it was obtained as light blue solid, mp: 173-174 ^{o}C. IR (cm^{-1}): 1715 (C=O), 1670 (C=N), 1265 (C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.2-2.3 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 2.4 [s, 3H, Ar-C$\underline{H}_3$], 3.4 [s, 2H, O=C-C$\underline{H}_2$-], 3.5[t, 1H, Ar-C$\underline{H}$- CH_2-], 3.7-3.9 [s, 6H, Ar-OC$\underline{H}_3$-x 2], 5.3-5.4 [br,1H, -N$\underline{H}$-C=O], 6.8-7.0 [m, 4H, aromatic], 7.1 [m, 3H, aromatic], 7.5 [m, 2H, aromatic], 7.6 [m, 1H, aromatic], 8.2 [m, 1H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 25.7 (CH_3), 40.9 (CH_2), 51.8 (CHN), 56.0 (CH_2N), 56.2 (OCH_3), 56.5 (OCH_3), 107.2 (C=C), 114.2, 115.9, 123.2, 126.2 (C=CS), 127.5 (C=C), 129.9, 130.3, 131.4, 136.9, 137.7, 142.9 (C=CN), 152.8 (C=N), 157.9 (C=CO), 163.0 (C=CO), 169.7 (C=O), 175.9 (N=CNH). Mass spectrum (LCM): m/z 486 $[M]^+$ for $C_{27}H_{26}N_4O_3S$. Elemental Analysis: Calculated: %N: 11.51, %C: 66.65, %H: 5.39, %S: 6.59. Observed: %N: 11.48, %C: 66.70, %H: 5.51, %S: 6.65.

2-(4,5-dihydro-3-(4-methoxyphenyl)-5-p-tolylpyrazol-1-yl)-_N_-(6-nitrobenzothiazol-2-yl) acetamide (6c):

Yield 65%; it was obtained as yellow solid, mp: 238-239 ^{o}C. IR (cm^{-1}): 1720 (C=O), 1675 (C=N), 1360 (NO_2), 1260 (C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.2 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 2.4 [s, 3H, Ar-C$\underline{H}_3$], 3.4 [s, 2H, O=C-C$\underline{H}_2$-], 3.5[t, 1H, Ar-C$\underline{H}$- CH_2-], 3.7-3.9 [s, 3H, Ar-OC$\underline{H}_3$-], 5.3-5.4 [br, 1H, -N$\underline{H}$-C=O], 6.8-7.0 [m, 4H, aromatic], 7.0-7.2 [m, 2H, aromatic], 7.5-7.7 [m, 2H, aromatic], 7.9-8.1 [m, 2H, aromatic], 8.5 [s, 1H, aromatic]. ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 25.6 (CH_3), 40.2 (CH_2), 51.3 (CHN), 56.2 (CH_2N), 56.3 (OCH3), 115.8 (C=C), 116.9, 123.2, 123.5, 126.5 (C=CS), 127.5 (C=C), 129.2, 130.2, 131.3, 137.4, 137.5, 147.2 (C=CNO_2), 152.3 (C=N), 157.2 (C=CN), 163.2 (C=CO), 169.9 (C=O), 175.7 (N=CNH). Mass spectrum (LCM): m/z 518 $[M+NH_4]^+$ for $C_{26}H_{23}N_5O_4S$,. Elemental Analysis: Calculated: %N: 13.96, %C: 62.26, %H: 4.62, %S: 6.39. Observed: %N: 13.85, %C: 62.40, %H: 4.35, %S: 6.85.

_N_-(benzothiazol-6-yl)-2-(4,5-dihydro-3-(4-methoxyphenyl)-5-p-tolylpyrazol-1-yl)acetamide (6d):

Yield 76%; it was obtained as white solid, mp: 180-181 ^{o}C. IR (cm^{-1}): 1720 (C=O), 1675 (C=N), 1260 (C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.2-2.3 [dd, 2H, Ph-CH-C$\underline{H}_2$-], 2.4 [s, 3H, Ar-C$\underline{H}_3$], 3.4 [s, 2H, O=C-C$\underline{H}_2$-], 3.5[t, 1H, Ar-C$\underline{H}$- CH_2-], 3.7-3.9 [s, 3H, Ar-OC$\underline{H}_3$-], 5.3-5.4 [br, 1H, -N$\underline{H}$-C=O], 6.8-7.0 [m, 4H, aromatic], 7.0-7.2 [m, 2H, aromatic], 7.5-7.7 [m, 2H, aromatic], 8.3 [m, 3H, aromatic], 9.2 [s, 1H, aromatic].

^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 25.5 (CH_3), 40.8 (CH_2), 51.3 (CHN), 56.3 (OCH_3), 56.5 (CH_2N), 115.2 (C=C), 121.2, 124.2, 127.2, 129.3, 129.8, 131.5, 136.2 (C=CS), 136.5 (C=C), 137.9, 151.2 (C=CN), 152.4 (C=N), 156.5 (SC=N), 163.5 (C=CO), 169.3 (C=O). Mass spectrum (LCM): m/z 456 $[M^+]$ for $C_{26}H_{24}N_4O_2S$. Elemental Analysis: Calculated: %N: 12.27, %C: 68.40, %H: 5.30, %S: 7.02. Observed: %N: 12.15, %C: 68.45, %H: 5.35, %S: 7.25.

MTT assay:

MCF-7 (Breast cancer cell lines) and Hep G-2 (Liver cancer cell lines) Cells were grown in monolayer cultures in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 5% foetal bovine serum, 100 µg /mL penicillin, 10 µg/mL streptomycin and maintained at 37^{o}C in a 5% CO_2 incubator. The cells were washed

with PBS (phosphate buffer saline) and harvested by tripsinization. The cells were plated (10^4 cell/well) in 96-well plates, and incubated over night at 37°C in the incubator.

They were exposed to different concentrations of the compounds synthesized (**1a-6d**) for further 72 h. At the end of this period MTT assay as described below was performed[14].

This assay measures the metabolism of 3-(4,5-dimethylthiazol-2yl)-2,5-biphenyl tetrazolium bromide to form an insoluble formazan precipitated by mitochondrial dehydrogenases, which are present only in viable cells. 10 µL of MTT stock solution (5 mg MTT dissolved in 1 mL of incomplete media) was added in each well of the 96-well plate and incubated at 37 °C for 3 h followed by the removal of the medium by aspiration and addition of 100 µL DMSO per well. The plate was shaken for 1h and the absorbance at 570 nm is measured using ELISA micro titer plate reader. Viability was defined as the ratio (expressed as a percentage) of absorbance of treated cells to untreated cells that served as control [14-15].

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