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FOUR-COMPONENT SYNTHESIS OF FUNCTIONALIZED 1, 3, 4-OXADIAZOLE DERIVATIVES BEARING THE 2-AMINOBENZOTHIAZOLE MOIETY

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Abstract – A one-pot eighteen derivatives of N-((5-(aryl)-4*H*-pyrazol-3-yl)(aryl)methyl)benzo[*d*]thiazol-2-amine (**5a–r**) were synthesized from 2-aminobenzothiazole, aromatic aldehyde, N-isocyaniminotriphenylphosphorane on reaction with aryl carboxylic acid derivatives under a catalyst-free condition in CH_2Cl_2 by a Ugi-4CR/*aza*-Wittig cyclization at room temperature in fairly good yields (except for **5r**, in which the aldehyde used has an electron-donating group). The newly synthesized compounds were confirmed and deduced based on IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy, and elemental analysis.

INTRODUCTION

In the last few decades, the chemistry of isocyanides has significant development and influence on the evaluation of novel utilization in medicinal chemistry and chemical methodologies.[1] The discovery of novel isocyanide-based multicomponent reactions (IMCRs) can be considered as an interesting research topic that also satisfied the practical interest of applied science.[2-5] The utility of IMCRs in assembling complex pharmacologically important structures in a small number of steps and with the possibility of several diverse inputs is widely recognized.[6-10] Meanwhile, N-isocyaniminotriphenylphosphorane (NIITP) is expected to have a synthetic potential compound because it can cause a reaction in which the iminophosphorane group reacts with a reagent which have a carbonyl functionality. NIITP, due to its unique specification and structure plays a considerable role in numerous approaches in the multicomponent reactions (MCRs), organometallic compounds, and heterocyclic chemistry. Furthermore,

NIITP cooperates in the intramolecular version of the *aza*-Wittig type transfiguration because of its high potential for the synthesis of nitrogen heterocycles like functionalized 1,3,4-oxadiazoles.[11-17]

On the other hand, the existence of 2-aminobenzothiazole and 1,3,4-oxadiazoles fraction in natural or synthetic products represent the important rings that have been described with a broad-spectrum of pharmaceutical applications such as antitumor,[18-20] antitrypanosomal,[21] antibacterial,[22] antiviral activity[23] and adenosine receptor.[24]

For example, compound **A** evaluated for its antioxidant and anti-inflammatory activities.[25] Compound **B** exhibited antifungal activity through the inhibition of ergosterol biosynthesis.[26] Compounds **C** and **D** showed antitumor activity against leukemia cell lines.[27] Compound **E** displayed a higher affinity to inhibit the COX-2 enzyme (Figure 1).[28]

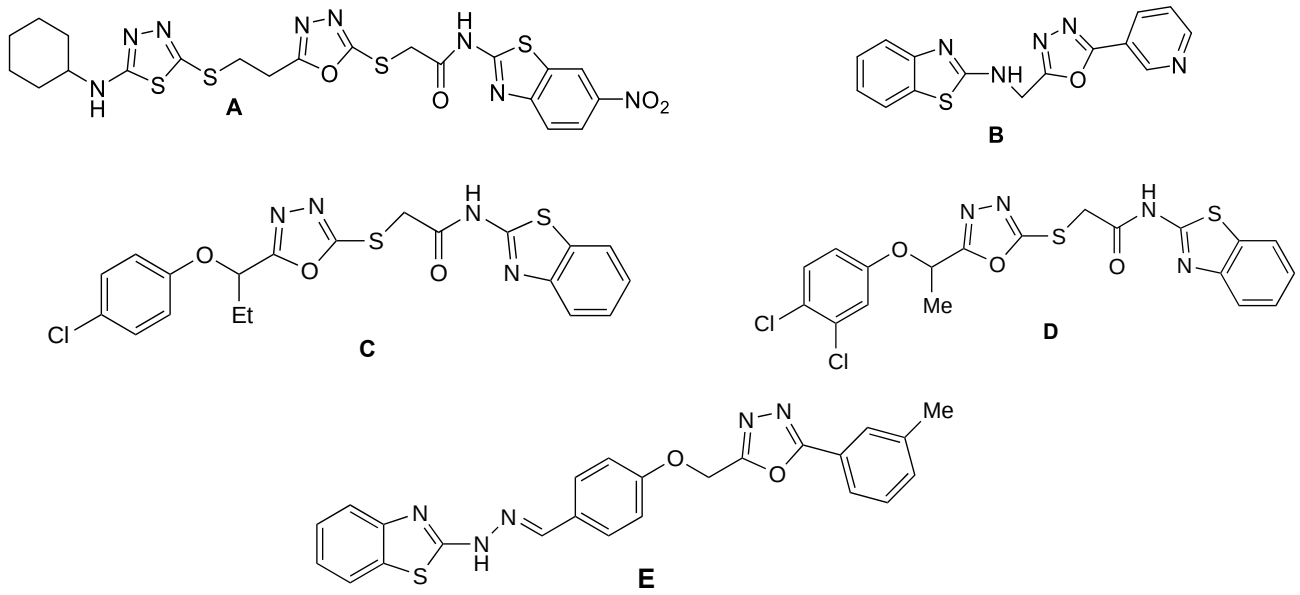
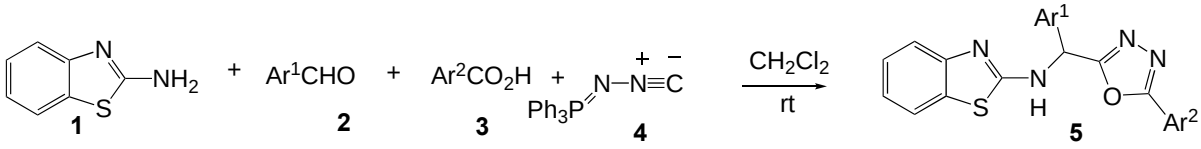


Figure 1. Structures of compounds A-E

All the procedures for the synthesis of these compounds are multi-steps by the cyclization of hydrazides with a variety of reagents such as thionyl chloride, phosphorus oxychloride, or sulfuric acid, usually under harsh reaction conditions. Ramezani and his co-workers have described the preparation of 1,3,4-oxadiazole derivatives via a one-pot four-component reaction of carbonyl compounds, alkyl amines, carboxylic acids, and N-isocyaniminotriphenylphosphorane (NIITP).[29-33] In this work, the methodology was extended by employing 2-aminobenzothiazole as aromatic amine (Scheme 1).



2	Ar^1
a	C_6H_5
b	3-NO_2-C_6H_4
c	4-NO_2-C_6H_4
d	4-Cl-C_6H_4
e	4-MeO-C_6H_4

3	Ar^2
a	C_6H_5
b	4-NO_2-C_6H_4
c	4-Cl-C_6H_4
d	4-F-C_6H_4
e	4-Br-C_6H_4
f	4-Cl,3-NO_2-C_6H_3
g	4-MeO-C_6H_4

Scheme 1. A typical procedure for the synthesis of **5**

RESULTS AND DISCUSSION

At first, we optimized the condition of the reaction (Table 1). For this purpose, we considered the reaction of 2-aminobenzothiazole (**1**), benzaldehyde (**2a**), benzoic acid (**3a**), and N-isocyaniminotriphenylphosphorane (**4**) as a template. This reaction was performed in different solvents such as THF, MeCN, EtOH, CH_2Cl_2, DMF, and toluene and catalyst-free conditions for 4 hours. The best result was observed for dichloromethane with a 35% yield (Entry 6, Table 1). After that, we investigated the effect of temperature on increasing the efficiency of the reaction. Therefore, this reaction was carried out in MeCN, DMF, and toluene under reflux conditions for 4 hours. No positive changes occurred in the yield of **5a** (Entry 8-10, Table 1). Then we increased the reaction time to 8 h. Notably, the yield of the desired product (**5a**) in dichloromethane increased significantly (Entry13, Table 1). Therefore, due to the applied conditions, we explored the reaction in dichloromethane with different derivatives of benzaldehydes (**2a**), benzoic acids (**3a**) as starting materials.

Table 1. Optimization of reaction conditions

entry	solvent	Time (h)	Temperature (°C)	Yield of **5a** (%)
2	toluene	4	25	35
3	MeCN	4	25	39
4	EtOH	4	25	34
5	THF	4	25	15
6	CH_2Cl_2	4	25	42
7	DMF	4	25	28
8	toluene	4	reflux	58
9	MeCN	4	reflux	43
10	DMF	4	reflux	52
11	EtOH	8	25	47
12	THF	8	25	29
13	**CH_2Cl_2**	**8**	**25**	**87**
14	toluene	8	reflux	66
15	MeCN	8	reflux	59
16	DMF	8	reflux	71

The results for the generation of compound **5** are summarized in Figure 2. For the characterization of the newly synthesized compounds, the ^{1}H and ^{13}C NMR, IR, mass, and elemental analysis techniques were used. Following IR spectra of the synthesized derivatives (**5a-r**), the existence of NH group was approved by the absorption at about 3300 cm^{-1} appearing due to NH stretching. The presence of NH group was additionally verified by the appearance of a typical broad singlet of one proton between 6.00-8.50 ppm in ^{1}H NMR spectra that disappeared after the addition of D_2O to the acetone (d_6) solution. Further, in ^{1}H NMR spectra of compounds (**5a-r**), the signal for aliphatic methine proton was displayed as singlet appearing in the range 5.48-6.43 ppm amalgamating for one proton while the signal for this carbon atom is presented in the ^{13}C NMR spectra at 54.9-69.1 ppm. In ^{1}H NMR spectra of **5a-r**, the aromatic protons resonated at 6.92-8.91 ppm. Also, in ^{13}C NMR spectra of compounds (**5a-r**) the signals which are arisen from oxadiazole moiety are observed between 159.9-166.8 ppm and 163.2-167.9 ppm, respectively. No phosphorus signal was found in the ^{31}P NMR spectrum of **5a**. When the reaction was performed by *p*-methoxybenzaldehyde (**2e**), the yield of product is reduced significantly due to the positive inductive effect of electron-donating substituent and decrease the reactivity of carbonyl group.

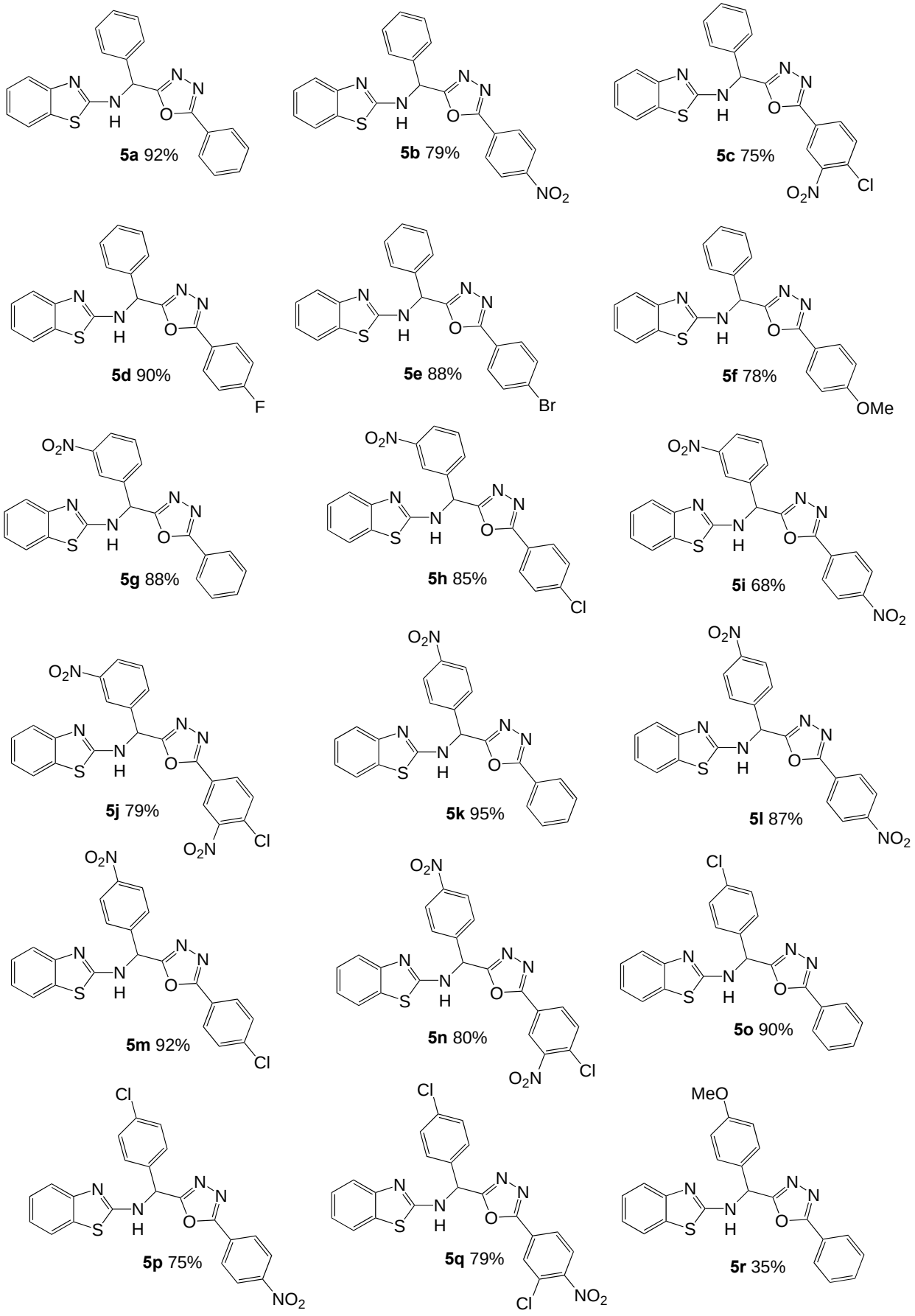
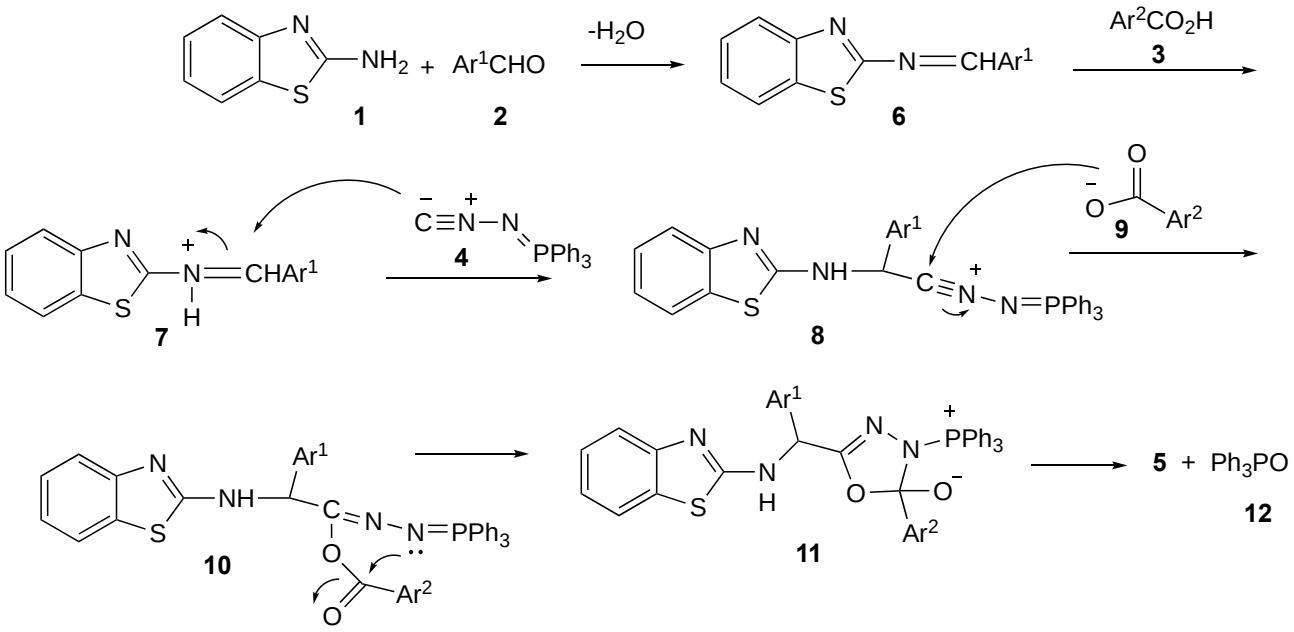


Figure 2. Synthesis of compounds **5a-r**

Mechanistically, it is conceivable that the first step is condensation reaction between aldehyde **2** and 2-aminobenzothiazole (**1**) to generate the imine intermediate **6** which is protonated by aromatic carboxylic acid **3** to afford iminium ion **7**. Next, the *N*-isocyaniminotriphenylphosphorane (**4**) attack by nucleophilic addition to **7** that leads to nitrilium intermediate **8**. After that, the 1:1:1:1 adduct **10** is formed by the addition of the conjugate base of the aromatic acid **9** to intermediate **11**. The intramolecular *aza*-Wittig reaction is occurred by this adduct through the ester carbonyl group with the iminophosphorane moiety and finally by the elimination of triphenylphosphine oxide (**12**) and the compound **5** is produced (Scheme 2).



Scheme 2. A plausible mechanism for formation of **5**

In summary, isocyanide-based multicomponent reactions (I-MCRs) successfully promoted a convenient and simple method for the one-pot four-component catalyst-free intramolecular *aza*-Wittig synthesis of *N*-((5-(aryl)-4*H*-pyrazol-3-yl)(aryl)methyl)benzo[*d*]thiazol-2-amine. Based on our literature survey, this is the first report in which N-isocyaniminotriphenylphosphorane (NIITP) is utilized in the presence of (benzothiazol-2-yl)arylmethanimine and aromatic acids to produce the ring closure. Notable features of the current methodology include simplicity in the workup, easy availability of synthetic methods, mild and neutral reaction conditions for the cyclization, readily available reagents, and a reduction in the number of synthesis steps. Further investigations for evaluation of their antioxidant, anti-inflammatory, and antitumor activities are in progress. Additional works are also including the use of other aromatic amine precursors.

EXPERIMENTAL

All starting materials were used as collected from Merck, Fluka, Aldrich, and TCM. The employed solvents were purified and dried by standard procedures before use. Melting points were measured on an electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR- 460 spectrometer using KBr discs. ^{1}H, ^{13}C, and ^{31}P NMR spectra were registered on a Bruker DRX-300, Avance spectrometer at 300, 75.5, and 121 MHz, respectively. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured in acetone (d_6), using TMS as the internal standard. EI-MS (70 eV) was done on a Finnigan MAT-8430 mass spectrometer and accorded in *m/z*. Elemental analysis was performed with a Heraeus CHN-O-Rapid Analyzer. Final purifying was observed by thin-layer chromatography (TLC) on precoated silica gel 20×20 cm glass plates (60 GF254, 0.25mm thickness, Merck) envisioned under a UV lamp. The names of all the compounds were found out on ChemDraw.

General procedure for the preparation of compounds (5a-r)

A solution of aromatic carboxylic acid (2 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a magnetically stirred solution of 2-aminobenzothiazole (2 mmol), aromatic aldehyde (2 mmol), and N-isocyaniminotriphenylphosphorane (2 mmol) in CH_2Cl_2 (5 mL) over 5 min. Then the mixture was stirred for 8 h at room temperature. At the end of the process (screened by thin-layer chromatography (silica gel; hexane: EtOAc, 3:1 as eluent)), the solvent was removed by rotary under reduced pressure. The residual of the reaction was purified by the TLC technique at the previously mentioned condition.

***N*-(Phenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methyl)benzo[*d*]thiazol-2-amine (5a):** Yellow viscous oil, Yield 0.70 g (92%). IR (KBr), (ν_{max}, cm^{-1}): 3298, 3117, 2973, 2928, 1629, 1532, 1446, 1286, 753. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.73 (s, 1H, CH), 6.74 (brs, 1H, NH), 7.25-7.52 (m, 5H, 5CH), 7.56-7.78 (m, 5H, 5CH), 7.95-8.05 (m, 3H, 3CH) 8.22-8.27 (m, 1H, 1CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 68.2 (CH), 119.1, 121.5, 122.0, 124.7, 126.2, 127.3, 128.0, 128.3, 129.2, 129.5, 130.0, 132.3, 140.2, 153.8 (Ph-C), 167.3 and 168.1 (2C=N$_{oxadiazole}$), 173.7 (S-C=N). MS (EI) *m/z*: 384 (M$^+$, 71), 325 (15), 277(28), 251 (31), 237 (98), 177(42), 163 (30), 150 (100), 105 (83). Anal. Calcd for $C_{22}H_{16}N_4OS$ (384.10):C, 68.73; H, 4.20; N, 14.57; S, 8.34. Found: C, 68.70; H, 4.23; N, 14.55; S, 8.31.

***N*-((5-(4-Nitrophenyl)-1,3,4-oxadiazol-2-yl)(phenyl)methyl)benzo[*d*]thiazol-2-amine (5b):** Yellow viscous oil, Yield 0.67 g (79%). IR (KBr), (ν_{max}, cm^{-1}): 3409, 3190, 2925, 2853, 1698, 1526, 1384, 1093.^{1}H NMR (300 MHz, acetone-d_6) δ 6.23 (s, 1H, CH), 6.74 (brs, 1H, NH), 7.02 (t, *J* = 7.6 Hz, 1H, CH), 7.21 (t, *J* = 7.8 Hz, 2H, 2CH), 7.34-7.45 (m, 2H, 2CH), 7.50-7.76 (m, 2H, 2CH), 7.96 (d, *J* = 7.9 Hz, 1H, CH), 8.30 (d, *J* = 8.9 Hz, 3H, 3CH), 8.45 (d, *J* = 8.9 Hz, 2H, 2CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 62.3 (CH), 118.9, 123.3, 124.7, 125.2, 126.2, 127.4, 129.3, 129.7, 132.7, 135.2, 135.7, 138.8, 145.8, 152.7 (Ph-C), 163.9 and 164.7 (2C=N$_{oxadiazole}$), 170.9 (S-C=N). MS (EI) *m/z*: 429 (M$^+$, 42), 352 (25), 307 (33), 280 (46), 239 (82), 190 (51), 149 (79), 77 (84). Anal. Calcd for $C_{22}H_{15}N_5O_3S$ (429.09): C, 61.33; H,

3.52; N, 16.31; S, 7.47. Found: C, 61.57; H, 3.53; N, 16.28; S, 7.44.

***N*-((5-(4-Chloro-3-nitrophenyl)-1,3,4-oxadiazol-2-yl)(phenyl)methyl)benzo[*d*]thiazol-2-amine (5c):** Yellow viscous oil, Yield 0.69 g (75.5%). IR (KBr), (ν_{max}, cm^{-1}): 3304, 3174, 2956, 2927, 1630, 1534, 1446, 1384, 1120, 751. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.62 (s, 1H, CH), 7.52-7.60 (m, 4H, 4CH), 7.87-7.94 (m, 4H, 4CH), 8.20-8.23 (m, 3H, 3CH), 8.50 (s, 1H, NH), 8.91 (s, 1H, CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 54.9 (CH), 118.1, 121.7, 122.5, 123.2, 123.7, 125.5, 126.6, 127.4, 129.3, 129.9, 133.0, 133.6, 139.2, 141.1, 144.9, 158.2 (Ph-C), 159.9 and 163.2 (2C=$N_{oxadiazole}$), 178.8 (S-C=N). MS (EI) *m/z*: 463 (M^+, 37), 329 (86), 314 (36), 307 (28), 252 (62), 239 (59), 224 (100), 158 (27), 155 (56), 77 (74). Anal. Calcd for $C_{22}H_{14}ClN_5O_3S$ (463.05):C, 56.96; H, 3.04; N, 15.10; S, 6.91. Found: C, 56.79; H, 3.05; N, 15.14; S, 6.94.

***N*-((5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl)(phenyl)methyl)benzo[*d*]thiazol-2-amine (5d):** Yellow viscous oil, Yield 0.72 g (90%). IR (KBr), (ν_{max}, cm^{-1}):3408, 3064, 2924, 2852, 1628, 1384, 1118. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.73 (s, 1H, CH), 6.73 (s, 1H, NH), 6.92 (d, J = 6.7 Hz, 1H, CH), 7.03 (t, J = 7.2 Hz, 1H, CH), 7.22-7.48 (m, 4H, 4CH), 7.61-7.79 (m, 3H, 3CH), 7.09-8.05 (m, 4H, 4CH), ^{13}C NMR (75.5 MHz, acetone-d_6) δ 67.9 (CH), 116.8 (d, $^2J_{C\text{-}F}$ = 22.7 Hz, 2CH), 118.8, 121.2, 121.7, 124.4, 125.9, 127.0, 128.7, 129.0 (Ph-C), 129.7 (d, $^3J_{C\text{-}F}$ = 9.1 Hz, 2CH), 132.0, 139.9, 153.5 (Ph-C), 163.5 (d, $^1J_{C\text{-}F}$ = 249.3 Hz, C-F), 164.4 and 167.1 (2C=$N_{oxadiazole}$), 167.9 (S-C=N). MS (EI) *m/z*: 402 (M^+, 24), 253 (17), 237 (14), 150 (80), 123 (100), 108 (18), 95 (37), 64 (38). Anal. Calcd for $C_{22}H_{15}FN_4OS$ (402.10): C, 65.66; H, 3.76; N, 13.92; S, 7.97. Found: C, 65.46; H, 3.77; N, 13.86; S, 7.96.

***N*-((5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)(phenyl)methyl)benzo[*d*]thiazol-2-amine (5e):** Yellow viscous oil, 0.81 g (88%). IR (KBr), (ν_{max}, cm^{-1}): 3416, 3149, 2924, 2851, 1678, 1586, 1316, 758. ^{1}H NMR (300 MHz, acetone-d_6) δ 6.19 (s, 1H, CH), 7.04 (brs, 1H, NH), 7.32-7.44 (m, 1H, CH), 7.60 (d, J = 7.5 Hz, 2H, 2CH), 77.70 (d, J = 8 Hz, 2H, 2CH), 7.76-7.83 (m, 2H, 2CH), 7.93-8.05 (m, 6H, 6CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 55.5 (CH), 113.1, 120.2, 122.6, 123.0, 123.7, 123.9, 126.8, 127.3, 127.9, 129.4, 132.5, 133.3, 141.6, 154.7 (Ph-C), 165.3 and 166.5 (2C=$N_{oxadiazole}$), 170.0 (S-C=N). MS (EI) *m/z*: 464 (M^++2, 90), 462 (M^+, 83), 313 (7), 225 (4), 183 (100), 154 (47), 105 (16), 75.5 (52). Anal. Calcd for $C_{22}H_{15}BrN_4O_5$ (462.01): C, 57.03; H, 3.26; N, 12.09; S, 6.92. Found: C, 56.99; H, 3.27; N, 12.11; S, 6.90.

***N*-((5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)(phenyl)methyl)benzo[*d*]thiazol-2-amine (5f):** Yellow viscous oil, Yield 0.64 g (78%). IR (KBr), (ν_{max}, cm^{-1}): 3363, 3242, 2924, 2856, 1690, 1640, 1531, 1346, 1094, 725. ^{1}HNMR (300 MHz, acetone-d_6) δ 3.85 (s, 3H, OCH_3), 5.76 (s, 1H, CH), 6.73 (brs, 1H, NH), 6.95 (d, J = 7.8 Hz, 2H, 2CH), 7.23-7.83 (m, 7H, 7CH), 7.96 (d, J = 7.8 Hz, 2H, 2CH), 8.03 (d, J = 6.8 Hz, 1H, CH), 8.30 (d, J = 8.5 Hz, 1H, CH). ^{13}CNMR (75 MHz, acetone-d_6) δ 54.8 (OCH_3), 68.4 (CH), 114.9, 116.0, 118.6, 118.9, 122.8, 124.5, 125.4, 126.5, 127.1, 128.7, 130.8, 142.7, 154.3 (Ph-C), 159.4, 162.3 and 165.1 (2C=$N_{oxadiazole}$), 171.6 (S-C=N). MS (EI) *m/z*: 414 (M^+, 17), 393 (8), 279 (7), 245(5), 167

(28), 149 (100), 138 (55), 111 (31), 57 (86), 45 (81). Anal. Calcd for $C_{23}H_{18}N_4O_2S$ (414.12): C, 66.65; H, 4.38; N, 13.52; S, 7.73. Found: C, 66.64; H, 4.39; N, 13.51; S, 7.72.

***N*-((3-Nitrophenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methyl)benzo[*d*]thiazol-2-amine (5g):** Yellow viscous oil, Yield 0.75 g (88 %). IR (KBr), (ν_{max}, cm^{-1}): 3386, 3079, 2957, 2926, 1608, 1536, 1349, 1052. ^{1}H NMR (300 MHz, acetone-d_6) δ 6.43 (s, 1H, CH), 6.74 (brs, 1H, NH), 7.20-7.60 (m, 6H, 6CH), 7.64-7.78 (m, 1H, CH), 7.92-8.06 (m, 3H, 3CH), 8.25 (d, *J* = 8Hz, 2H, 2CH), 8.45-8.76 (m, 1H, CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 67.1 (CH), 117.0, 122.0, 122.2, 123.9, 124.7, 124.9, 126.2, 127.5, 130.1, 130.7, 131.0, 132.7, 133.8, 138.1, 142.4, 154.3 (Ph-C), 162.1 and 167.4 (2C=$N_{oxadiazole}$), 179.8 (S-C=N). MS (EI) *m/z*: 429 (M^+, 58), 297 (12), 201 (6), 145 (50), 105 (100) 77 (84), 43 (34). Anal. Calcd for $C_{22}H_{15}N_5O_3S$ (429.09): C, 61.53; H, 3.52; N, 16.31; S, 7.47. Found: C, 61.56; H, 3.53; N, 16.27; S, 7.44.

***N*-((5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)(3-nitrophenyl)methyl)benzo[*d*]thiazol-2-amine (5h):** Yellow viscous oil, Yield 0.78 g (85%). IR (KBr), (ν_{max}, cm^{-1}): 3370, 3242, 2957, 2925, 1679, 1533, 1384, 726. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.99 (s, 1H, CH), 6.73 (brs, 1H, CH), 7.03 (d, *J* = 7.8 Hz, 1H, CH), 7.20-7.43 (m, 1H, CH), 7.46-7.61 (m, 2H, 2CH), 7.63-7.84 (m, 3H, 3CH), 7.93-8.05 (m, 3H, 3CH), 8.21-8.30 (m, 2H, 2CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 66.0 (CH), 112.4, 122.1, 122.7, 123.0, 124.3, 124.9, 125.2, 126.2, 128.7, 129.5, 130.1, 131.4, 133.7, 140.9, 145.5, 154.0 (Ph-C), 164.7 and 166.0 (2C=$N_{oxadiazole}$), 174.4 (C). MS (EI) *m/z*: 474 (M^+, 19), 325 (43), 341 (28), 314 (65), 218 (91), 192 (58), 179 (32), 135 (77), 111 (100), 96 (57). Anal. Calcd for $C_{22}H_{14}ClN_5O_3S$ (463.05):C, 56.96; H, 3.04; N, 15.10; S, 6.91. Found: C, 57.07; H, 3.05; N, 15.05; S, 6.88.

***N*-((3-Nitrophenyl)(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methyl)benzo[*d*]thiazol-2-amine (5i):** Yellow viscous oil. Yield 0.66 g (68%). IR (KBr), (ν_{max}, cm^{-1}): 3391, 3247, 2923, 2853, 1659, 1527, 1352, 1065. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.51 (s, 1H, CH), 6.75.5 (NH), 7.66-7.71 (m, 2H, CH and NH), 7.90-8.47 (m, 11H, 11CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 54.9 (CH), 118.4, 119.7, 122.2, 123.4, 124.4, 127.1, 128.1, 129.7, 130.2, 131.3, 134.0, 136.5, 139.2, 143.1, 143.5, 152.1 (Ph-C), 161.7 and 164.8 (2C=$N_{oxadiazole}$), 170.9 (S-C=N). MS (EI) *m/z*: 474 (M^+, 19), 340 (59), 298. (37), 230 (71), 190 (40), 172 (100), 162 (76), 157 (63), 134 (81), 122 (76). Anal. Calcd for $C_{22}H_{14}N_6O_5S$ (474.07): C, 55.69; H, 2.97; N, 17.71; S, 6.76. Found: C, 55.58; H, 2.98; N, 17.67; S, 6.73.

***N*-((5-(4-Chloro-3-nitrophenyl)-1,3,4-oxadiazol-2-yl)(3-nitrophenyl)methyl)benzo[*d*]thiazol-2-amine (5j):** Yellow viscous oil, 0.80 g (79%). IR (KBr), (ν_{max}, cm^{-1}): 3388, 3270, 2925, 2854, 1654, 1530, 1350, 724, 542. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.48 (s, 1H, CH), 7.04 (s, 1H, NH), 7.53 (t, *J* = 7.1 Hz, 2H, 2CH), 7.60 (d, *J* = 6.8 Hz, 2H, 2CH), 7.64-7.72 (m, 3H, 3CH), 7.93 (d, *J* = 7.6 Hz, 2H, 2CH), 8.19 (d, *J* = 7.6 Hz, 1H, CH), 8.47 (s, 1H, CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 64.7 (CH), 116.2, 122.6, 123.4, 124.3, 125.5, 126.1, 126.6, 127.7, 128.1, 129.3, 129.5, 131.4, 132.6, 134.4, 142.5, 145.3, 146.7, 151.6 (Ph-C), 164.8 and 166.6 (2C=$N_{oxadiazole}$), 176.0 (S-C=N). MS (EI) *m/z*: 508 (M^+, 26), 386 (47), 359 (63),

352 (19), 284 (38), 230 (92), 223 (75), 162 (56), 156 (29), 149 (100), 135 (88), 122 (59), 81 (44). Anal. Calcd for $C_{22}H_{13}ClN_6O_5S$ (508.04): C, 51.92; H, 2.58; N, 16.51; S, 6.30. Found: C, 52.07; H, 2.58; N, 16.44; S, 6.32.

***N*-((4-Nitrophenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methyl)benzo[*d*]thiazol-2-amine (5k):** Yellow viscous oil, Yield 0.81 g (95%). IR (KBr), (ν_{max}, cm^{-1}): 3433, 3079, 2959, 2928, 1714, 1536, 1384, 1093, ^{1}H NMR (300 MHz, acetone-d_6) δ 6.43 (s, 1H, CH), 6.73 (brs, 1H, NH), 7.03-7.75.5 (m, 7H, 7CH), 7.95-8.06 (m, 2H, 2CH), 8.25 (d, *J* = 8.7 Hz, 1H, CH), 8.53-8.69 (m, 3H, 3CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 68.2 (CH), 114.9, 122.2, 123.9, 127.5, 129.6, 130.1, 130.7, 131.9, 132.7, 133.4, 133.8, 143.8, 149.3, 159.2 (Ph-C), 166.8 and 167.9 (2C=$N_{oxadiazole}$), 178.2 (S-C=N). MS (EI) *m/z*: 429 (M^+, 10), 349 (82), 320 (60), 311 (55), 150 (37), 105 (100), 51 (3). Anal. Calcd for $C_{22}H_{15}N_5O_3S$ (429.09): C, 61.53; H, 3.52; N, 16.31; S, 7.47. Found: C, 61.55; H, 3.51; N, 16.29; S, 7.46.

***N*-((4-Nitrophenyl)(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methyl)benzo[*d*]thiazol-2-amine (5l):** Yellow viscous oil, Yield 0.82 g (87%). IR (KBr), (ν_{max}, cm^{-1}): 3373, 3010, 2928, 2857, 1685, 1526, 1351, 1288, 1117. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.50 (s, 1H, CH), 6.0 (brs, 1H, NH), 7.64-7.77 (m, 4H, 4CH), 8.04 (d, *J* = 7.5 Hz, 1H, CH), 8.14-8.22 (m, 3H, 3CH), 8.35 (d, *J* = 8.6 Hz, 2H, 2CH), 8.48 (m, 2H, 2CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 68.2 (CH), 122.2, 123.4, 124.4, 129.5, 129.7, 130.3, 132.0, 133.4, 134.0, 139.1, 141.2, 143.5, 149.0, 153.9 (Ph-C), 165.0 and 167.9 (2C=$N_{oxadiazole}$), 171.1 (S-C=N). MS (EI) *m/z*: 474 (M^+, 96), 473 (36), 279 (3), 219 (2), 149 (36), 121 (6), 89 (40), 45 (100). Anal. Calcd for (474.07): C, 55.69; H, 2.97; N, 17.71; S, 6.76. Found: C, 55.65; H, 2.99; N, 17.68; 6.71.

***N*-((5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)(4-nitrophenyl)methyl)benzo[*d*]thiazol-2-amine (5m):** Yellow viscous oil, 0.85 g (92%). IR (KBr), (ν_{max}, cm^{-1}): 3194, 3115, 2928, 2851, 1684, 1530, 1346, 729. ^{1}H NMR (300 MHz, acetone-d_6) δ 6.43 (s, 1H, CH), 7.05 (brs, 1H, NH), 7.50 (d, *J* = 7.7 Hz, 2H, 2CH), 7.55-7.64 (m, 2H, 2CH), 7.70-7.76 (m, 2H, 2CH), 7.99-8.06 (m, 3H, 3CH), 8.23-8.26 (m, 1H, CH), 8.52-8.53 (m, 2H, 2CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 67.1(CH), 118.7, 122.2, 123.4, 124.0, 129.1, 129.2, 130.3, 130.7, 132.2, 133.8, 138.3, 138.8, 142.3, 149.3 (Ph-C), 165.1 and 167.6 (2C=$N_{oxadiazole}$), 181.0 (S-C=N). MS (EI) *m/z*: 463 (M^+, 19), (M^+ +2, 10), 418 (34), 401 (22), 395 (9), 331 (50), 179 (100), 111(76), 77 (44), 51 (23). Anal. Calcd for $C_{22}H_{14}ClN_5O_3S$ (463.05): C, 56.96; H, 3.04; N, 15.10; S, 6.91. Found: C, 56.93; H, 3.09; N, 15.07; S, 6.90.

***N*-((5-(4-Chloro-3-nitrophenyl)-1,3,4-oxadiazol-2-yl)(4-nitrophenyl)methyl)benzo[*d*]thiazol-2-amine (5n):** Yellow viscous oil, Yield 0.81g (80%). IR (KBr), (ν_{max}, cm^{-1}): 3270, 3092, 2950, 2927, 1662, 1534, 1351, 1096, 731. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.49 (s, 1H, CH), 7.02 (s, 1H, NH), 7.37-7.75.5 (m, 4H, 4CH), 7.85-8.04 (m, 3H, 3CH), 8.19 (d, *J* = 7.5 Hz, 1H, CH), 8.46 (s, 1H, 1CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 66.2 (CH), 118.9, 120.7, 121.5, 122.2, 123.4, 125.3, 125.4, 129.9, 130.3, 132.7, 133.0, 133.8, 134.0 (CH), 143.5, 148.8, 149.0 (Ph-C), 160.7 and 163.6 (2C=$N_{oxadiazole}$), 170.9 (S-C=N). MS (EI)

m/z: 508 (M^+,15), 374 (61), 359 (36), 284 (74), 218 (100), 203 (58), 141 (72), 134 (80), 122 (39), 46 (49). Anal. Calcd for $C_{22}H_{13}ClN_6O_5S$ (508.04):C, 51.92; H, 2.58; N, 16.51, S, 6.30. Found: C, 68.70; H, 4.23; N, 14.55; S, 8.31.

***N*-((4-Chlorophenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methyl)benzo[*d*]thiazol-2-amine (5o):** Yellow viscous oil, Yield 0.75 g (90%). IR (KBr), (ν_{max}, cm^{-1}): 3229, 3196, 2958, 2928, 1726, 1662, 1270, 746. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.76 (s, 1H, CH), 6.72 (brs, 1H, NH), 6.95 (d, *J* = 7.8 Hz, 2H, 2CH), 7.20-7.83 (m, 7H, 7CH), 7.96 (d, *J* =7.8 Hz, 1H, CH), 8.03 (d, *J* = 8.1Hz, 2H, 2CH), 8.23-8.32 (m, 1H, CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 69.1 (CH), 119.2, 121.5, 122.1, 125.1, 126.3, 127.2, 129.5, 129.7, 129.9, 130.8, 132.1, 133.2, 139.3, 154.9 (Ph-C), 164.9 and, 167.5 (2C=$N_{oxadiazole}$), 171.3 (S-C=N). MS (EI) *m/z*: 418 (M^+, 41), (M^+ +2, 26) 393 (55), 385 (37), 279 (9), 167 (28), 149 (100), 111 (31), 57 (91). Anal. Calcd for $C_{22}H_{15}ClN_4OS$ (418.07): C, 63.08; H, 3.61; N, 13.38; S, 7.65. Found: C, 62.89; H, 3.63; N, 13.43; S, 7.58.

***N*-((4-Chlorophenyl)(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methyl)benzo[*d*]thiazol-2-amine (5p):** Yellow viscous oil, Yield 0.69 g (75.5%). IR (KBr), (ν_{max}, cm^{-1}): 3416, 3210, 2925, 2854, 1663, 1528, 1384, 722. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.62 (s, 1H, CH), 7.12 (brs, 1H, NH), 7.39 (d, *J* = 8.2 Hz, 2H, 2CH), 7.49-7.73 (m, 5H, 5CH), 8.17 (d, *J* = 8.4 Hz, 3H, 3CH), 8.33 (d, *J* = 8.6 Hz, 2H, 2CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 62.9 (CH), 119.5, 121.7, 124.4, 127.3, 128.9, 129.4, 129.7, 130.4, 130.9, 131.7, 133.4, 138.6, 145.9, 150.5 (Ph-C), 162.7 and 167.0 (2C=$N_{oxadiazole}$), 172.3 (S-C=N). MS (EI) *m/z*: 463 (M^+, 18), 382 (66), 329 (41), 273(100), 207 (87), 230 (57), 134 (70), 122 (49). Anal. Calcd for $C_{22}H_{14}ClN_5O_3S$ (463.05): C, 56.96; H, 3.04; N, 15.10; S, 6.91. Found: C, 57.13; H, 3.03; N, 15.05; S, 6.88.

***N*-((5-(4-Chloro-3-nitrophenyl)-1,3,4-oxadiazol-2-yl)(4-chlorophenyl)methyl)benzo[*d*]thiazol-2-amine (5q):** Yellow viscous oil, Yield 0.78 g (79%). IR (KBr), (ν_{max}, cm^{-1}): 3370, 3243, 2959, 2929, 1645, 1532, 1350, 1275.5, 728. ^{1}H NMR (300 MHz, acetone-d_6) δ 6.26 (s, 1H, CH), 6.74 (s, 1H, NH), 6.97-7.07 (m, 2H, 2CH), 7.34-7.47 (m, 3H, 3CH), 7.59-7.65 (m, 1H, CH), 7.92-7.98 (m, 1H, CH), 8.25-8.31 (m, 2H, 2CH), 8.55-8.58 (m, 1H, CH), 8.65-8.70 (m, 1H, CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 61.8 (CH), 118.4, 122.4, 123.4, 125.0, 125.6, 126.2, 128.3, 129.2, 129.4, 130.8, 131.6, 133.0, 136.5, 140.7, 146.9, 155.3 (Ph-C), 162.5 and 167.8 (2C=$N_{oxadiazole}$), 170.1 (S-C=N). MS (EI) *m/z*: 497 (M^+, 26), 386 (61), 363 (38), 348 (73), 273 (29), 237 (57), 230 (44), 207 (100), 162 (69), 124 (52). Anal. Calcd for (497.01): C, 53.02; H, 2.63; N, 14.05; S, 6.43. Found: C, 52.81; H, 2.64; N, 14.09; S, 6.45.

***N*-((4-Methoxyphenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methyl)benzo[*d*]thiazol-2-amine (5r):** Yellow viscous oil, Yield 0.28 g (35%). IR (KBr), (ν_{max}, cm^{-1}): 3402, 3192, 2926, 2856, 1690, 1521, 1384, 1272, 1090, 752. ^{1}H NMR (300 MHz, acetone-d_6) δ 3.85(s, 3H, OCH_3), 5.73 (s, 1H, CH), 6.77 (brs, 1H, NH),

7.05 (d, *J* = 7.6 Hz, 2H, 2CH), 7.20-7.77 (m, 7H, 7CH), 7.91 (d, *J* = 7.9 Hz, 2H, 2CH), 8.02 (d, *J* = 8.0 Hz, 1H, CH), 8.25 (d, *J* = 8.3 Hz, 1H, CH). ^{13}C NMR (75.5 MHz, acetone-d_6) δ 55.5 (OCH_3), 68.0 (CH), 115.3, 118.4, 122.2, 123.4, 125.6, 126.2, 128.0, 128.3, 128.7, 129.2, 130.8, 136.5, 155.3 (Ph-C), 158.5, 162.5 and 165.36 (2C=$N_{oxadiazole}$), 171.2 (S-C=N). MS (EI) *m/z*: 414 (M^+, 11), 384 (4), 256 (6), 208 (8), 187 (12), 149 (100), 77 (64), 43 (28). Anal. Calc for $C_{23}H_{18}N_4O_2S$ (414.12): C, 66.65; H, 4.38; N, 13.52; S, 7.73. Found: C, 66.62; H, 4.40; N, 13.50; S, 7.72.

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