Green synthesis of 1,3,4-oxadiazole derivatives based on *N*-arylidene-2-(1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1*H*)-yl)acetohydrazide as potential antitumor agents

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Abstract:

Design of a new series of 1,3,4-oxadiazole derivatives was achieved in good yield *via* treatment of *N*-arylidene-2-(1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1*H*)-yl)acetohydrazide with cerium (IV) ammonium nitrate as a catalyst. They can be formulated also using one-pot reaction of 2-(1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1*H*)-yl)acetohydrazide, aromatic aldehyde and cerium (IV) ammonium nitrate in dichloromethane. The structural formulas of all synthesized products were elucidated based on their elemental and spectral analyses. In addition, MTT assay was used to evaluate antitumor activity of the synthesized molecules and some of them showed potent activity in comparison with Doxorubicin as a standard drug.

Keywords:

Phthalazine; hydrazide; cerium (IV) ammonium nitrate; oxadiazole; antitumor activity

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Introduction

Recently, cerium (IV) ammonium nitrate (CAN) gained great attention as one of the most convenient and widely used inexpensive catalysts for several types of chemical reactions. It is employed in the design of organic molecules *via* bond formation between two carbons or carbon and heteroatom [1-3]. In addition, easy handling, the low toxicity and good solubility of CAN in a large number of organic solvents increase its use as an efficient green catalyst [4]**.** On the other hand, 2,5-disubstituted-1,3,4-oxadiazoles constitute one of the most important class of nitrogen heterocyclic molecules, they possess a variety of biological effects including antibacterial [5-7], anti–inflammatory [8], antifungal [9], anticancer[10-14], antiviral [15] and antitubercular [16,17] activities. It was reported that, 1,3,4-oxadiazoles can be used also in various optoelectronic applications owing to their good blue fluorescent properties with better quantum yield [18,19].

Oxadiazole moiety can be formulated through different synthetic pathways. Among these, oxidation of acylhydrazone with oxidizing agents [20-22] or treatment of acid hydrazide with carboxylic acids and acid halide derivatives [23]. In addition, phthalazine derivatives were used as reactive starting targets in the design of novel biologically active molecules that exert potent antimicrobial [24-26], antitumor [27-30] analgesic and anti-inflammatory activities [31-33].

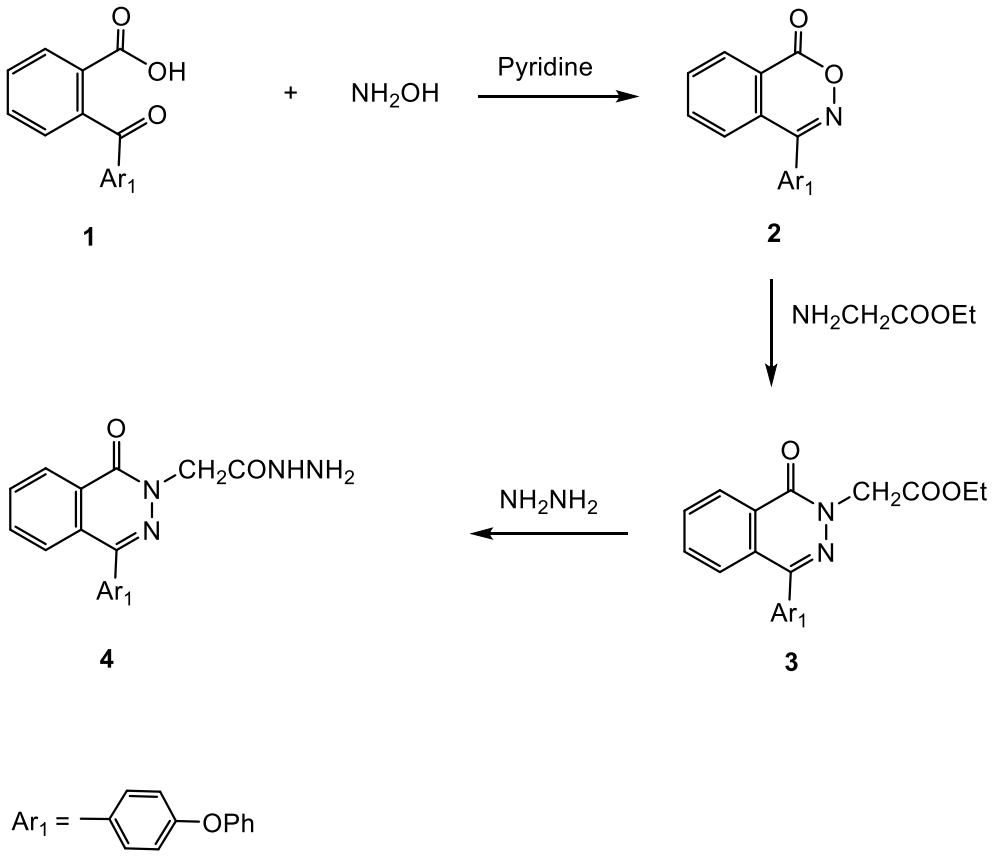
Based on the above mentioned observations and in continuation of our interest for synthesis of bio-active heterocyclic molecules [34-39], the present work deals with the synthesis of oxadiazole derivatives attached to phthalazine moiety in an attempt to obtain new molecules with potent antitumor activity.

Results and discussion

Synthesis of (1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1H)-yl)acetohydrazide **(4)** as the key compound in this work proceeded *via* the following steps. Initially, 2-(4-phenoxybenzoyl)benzoic acid **(1)** [prepared *via* Fridel- crafts acylation of diphenyl ether with phthalic anhydride in the presence of anhydrous aluminium chloride in tetrachloroethane as a solvent][30] was treated with hydroxyl amine in pyridine to give 4-(3-phenoxyphenyl)-1*H*-benzo[d][1,2]-oxazin-1-one **(2)**.

The structural formula of benzoxazinone **2** was confirmed on the basis of its spectral data and elemental analyses. IR spectrum showed characteristic bands at 1734, 1615 cm^{-1} corresponding to CO and C=N absorptions respectively. On the other hand, ^{1}H NMR spectrum confirmed disappearance of acidic proton in acid **1** and displayed only signals at 7.13-8.34 ppm corresponding to aromatic protons.

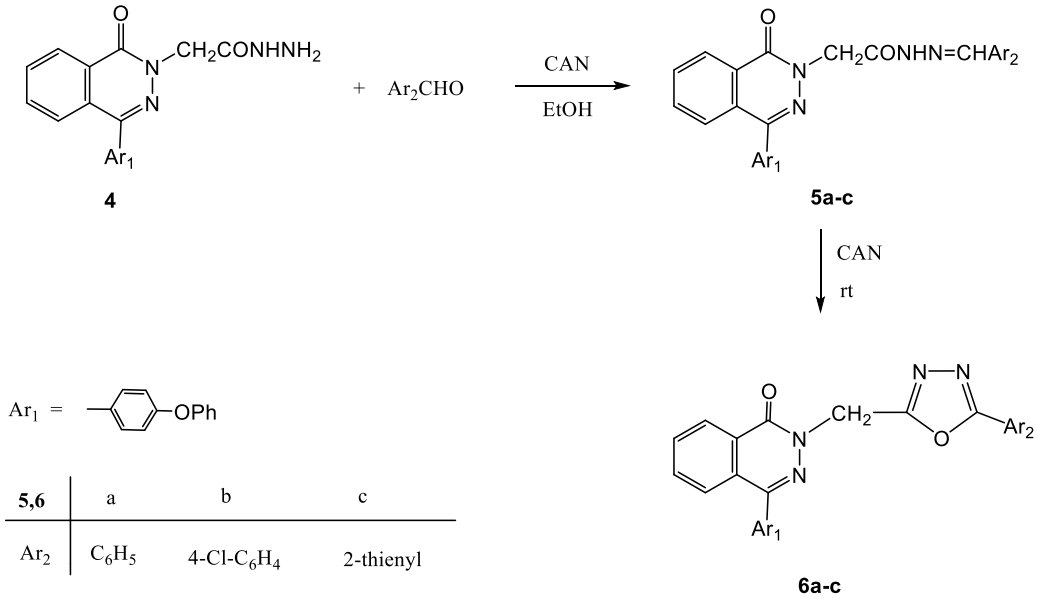
Benzoxazinone **2** reacted with ethyl glycinate in ethanol in the presence of sodium acetate to afford ester **3**. The latter reacted with hydrazine hydrate to give 2-(1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1*H*)-yl)acetohydrazide **(4), (**Scheme 1). IR spectrum of hydrazide **4** confirmed the presence of characteristic absorption bands of 2 CO, NH and NH_2 at 1684-1670 and 3447-3155 cm^{-1} respectively and disappearance of ester absorption band at 1733 cm^{-1}. ^{1}H NMR spectrum showed also signals at 12.80 and 7.13 ppm corresponding to NH and NH_2 protons respectively.



Scheme 1: Synthesis of 2-(1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1H)-yl)acetohydrazide **(4)**.

The hydrazide **4** was used as a reactive starting material to design a series of substituted 1,3,4-oxadiazole derivatives using cerium (IV) ammonium nitrate (CAN) as a catalyst followed by evaluation of their antitumor activity. Thus, it was allowed to react with aromatic aldehydes such benzaldehyde, 4-chlorobenzaldehyde and

thiophen-2-carboxaldehyde in ethanol in the presence of catalytic amounts of CAN to give the corresponding hydrazone **5a-c**. Grinding of hydrazones **5a-c** with CAN under solvent free conditions at room temperature resulted in formation of 2,5-diaryl-1,3,4-oxadiazole derivatives **6a-c**, (Scheme 2).



Scheme 2: Cyclization-oxidation reaction of hydrazones **5a-c** with cerium (IV) ammonium nitrate

The reaction was performed using different ratios of CAN (0.0001, 0.0005, 0.001, 0.005, 0.01 and 0.02 mol) to study the effect of the catalyst ratio on the yield of the produced oxadiazole. We observed higher yields of oxadiazole (73-87 %) in case of 0.01 mol and 0.02 mol of the catalyst but other ratios decreased the yields to lower than 60 %.

The conversion of hydrazone to oxadiazole moiety by the aid of CAN could be explained on the basis of cyclization-oxidation reaction of hydrazones **5a-c** that probably takes place according to the following mechanism, (Figure 1). As shown in the proposed mechanism CAN acts as an oxidant and Lewis acid [22].

According to the probable reaction mechanism, the carbonyl group of aldehyde could be activated by CAN to which hydrazide could be added by nucleophilic addition to form the hydrazone. The formation of oxadiazole moiety can be achieved *via* intermolecular cyclization of hydrazone. The coordination of Ce(IV) assists to activate C=N for nucleophilic addition of hydroxyl group to form intermediate X followed by removing of hydrogen to generate oxadiazole moiety.

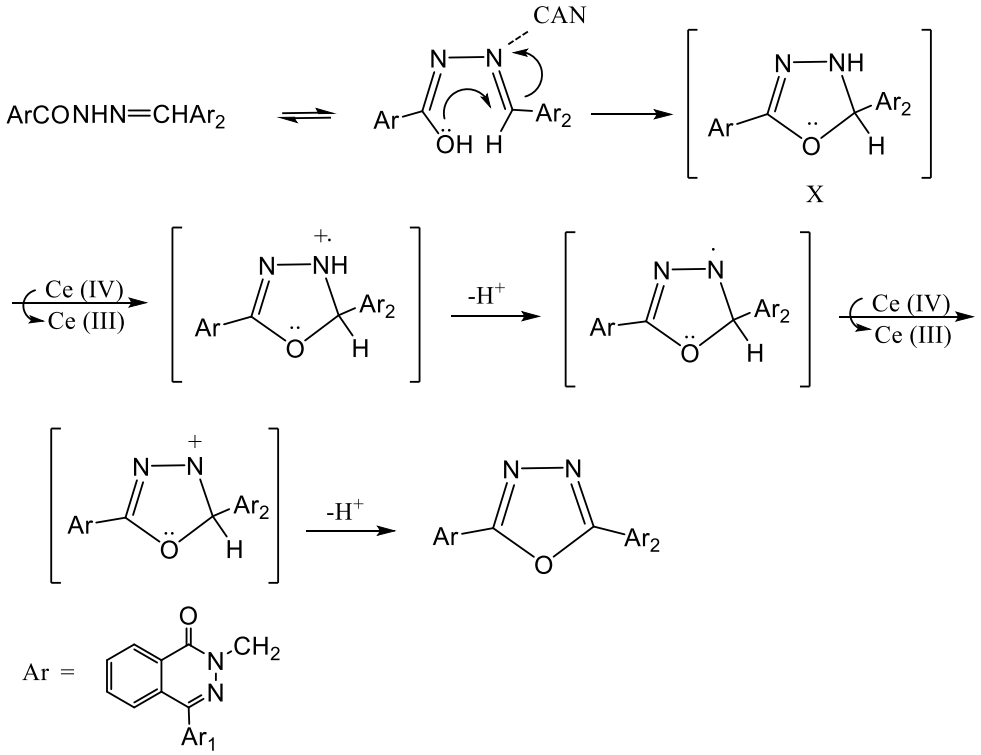
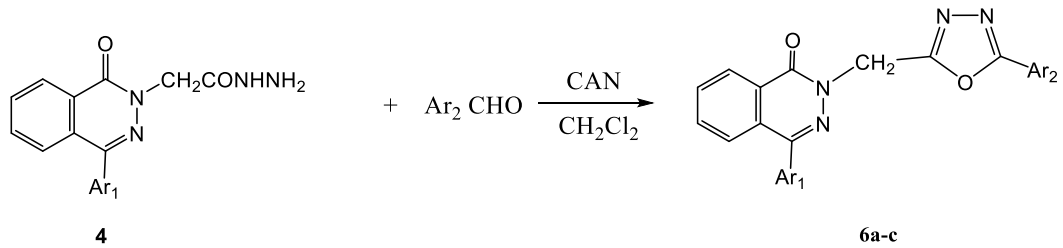
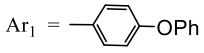


Figure 1: A proposed mechanism for the synthesis of oxadiazoles **6a-c.**

On the other hand, synthesis of oxadiazoles **6a-c** in high yields can be proceeded *via* one-pot reaction as alternative method involving 2-(1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1*H*)-yl)acetohydrazide **(4),** aromatic aldehydes and CAN in aqueous dichloromethane as a solvent, (Scheme 3).





6	a	b	c
Ar_2	C_6H_5	4-Cl-C_6H_4	2-thienyl

Scheme 3: One-pot synthesis of oxadiazoles **6a-c**

Antitumor activity:

Most of the synthesized molecules were screened for their *in vitro* cytotoxicity against four human tumor cell lines namely, hepatocellular carcinoma HePG-2, mammary gland breast cancer MCF-7, Human prostate cancer PC3 and Colorectal carcinoma HCT-116 using the colorimetric (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide) (MTT assay) [40,41]. The cell lines were obtained from ATCC via the Holding company for biological products and vaccines (VACSERA) (Cairo, Egypt). Doxorubicin was used as a standard cytotoxic drug for comparison.

MTT assay is used to determine cytotoxicity of potential medicinal agents and other toxic materials. It is colorimetric assay for measuring cell growth based on the conversion of the yellow tetrazolium bromide to a purple formazan derivative by mitochondrial succinate dehydrogenase in viable cells [41].

As shown in table 1, there are varying degrees of inhibitory activity toward the tested human tumor cell lines for the examined molecules in comparison with the standard Doxorubicin. Oxadiazole **6c** exhibited very strong cytotoxic activity among the studied series towards the tumor cell lines HePG-2, PC-3 and HCT-116 and strong activity towards MCF-7 with IC50 values 5.71, 7.26, 9.13 and 10.12 mg/mL respectively. Oxadiazole **6b** also showed strong activity towards HePG-2, MCF-7 and HCT-116 and very strong cytotoxic activity against PC3 with IC50 value 8.65 mg/mL. In addition, hydrazone **5c** revealed strong activity towards all the tested tumor cell lines having IC50 values 14.63, 20.48, 18.11 and 12.38 mg/mL. Other products showed cytotoxic activity that range from weak to moderate towards the tested cell lines.

It is observed from the given data, attachment of thiophene moiety in the hydrazone **5c** and oxadiazole **6c** and chlorophenyl group in oxadiazole **6b** enhanced their cytotoxic activity towards the tested tumor cell lines in comparison with the starting hydrazide **4** that exhibited only strong activity against PC3.

Table 1: Cytotoxic activity (IC50**) of some compounds against human tumor cells.**

Compounds	In vitro Cytotoxicity IC50 (μg/ml)•			
	HePG2	MCF-7	PC3	HCT-116
DOX•	4.50±0.2	4.17±0.2	8.87±0.6	5.23±0.3
3	52.01±4.0	42.65±3.5	69.22±4.5	26.22±2.3
4	28.22±3.2	24.13±3.2	19.35±1.9	36.52±2.2
5a	45.63±2.3	33.18±1.6	38.23±1.5	23.47±1.1
5b	29.41±2.5	53.44±3.9	32.09±2.9	40.30±3.5
5c	14.63±1.5	20.48±1.9	18.11±1.7	12.38±1.3
6a	34.52±3.1	36.97±3.4	47.04±3.8	16.13±1.7
6b	15.26±1.2	18.53±2.2	8.65±1.7	11.71±3.1
6c	5.71±0.4	10.12±1.1	7.26±0.8	9.13±1.0

• IC50 (μg/ml) : 1 – 10 (very strong). 11 – 20 (strong). 21 – 50 (moderate). 51 – 100 (weak) and above 100 (non-cytotoxic), • DOX : Doxorubicin

Conclusion

We have reported facile synthesis of 1,3,4-oxadiazole derivatives attached to phthalazinone moiety using *N*-arylidene-2-(1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1*H*)-yl)acetohydrazide as a reactive starting material in the presence of cerium (IV) ammonium nitrate as a catalyst. Most of the synthesized products were investigated also for their antitumor activities against four human tumor cell lines using MTT assay, compounds **5c, 6b** and **6c** showed the most potent cytotoxic effect as concluded from their IC50 values.

Experimental:

Melting points were measured in open capillaries using Gallen Kamp melting point apparatus and are uncorrected. NMR, IR, Mass spectra were carried out by Micro Analytical Unit at Cairo University. IR spectra were recorded on a JASCO IR 660 Plus spectrometer. NMR spectra were recorded on a Bruker Avance 400 (400 MHz) using DMSO as a solvent. Mass spectra (EI) were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer. All reactions were monitors by thin layer chromatography (TLC) and carried out on 0.2 mm silica gel 60 F254 (Mark) plates.

4-(4-Phenoxyphenyl)-1*H*-benzo[d][1,2]-oxazin-1-one (2)

A mixture of acid **1**[30] (0.01mol) and hydroxyl amine (0.01mol) in dry pyridine (20 mL) was refluxed for 6 hours. After cooling, the reaction mixture was poured on crushed ice/HCl, the precipitated solid was filtered off, washed, dried and crystallized from ethanol.

Yellowish white crystals, yield: 75 %; m.p. 120-122 ^{o}C. IR spectrum (KBr, ν, cm^{-1}): 1615 (C=N), 1734 (CO); ^{1}H NMR (DMSO-d_6, δ ppm): 7.13-7.54 (m, 9H, diphenylether-H), 7.65 -8.34 (m, 4H, benzoxazine-H); ^{13}C NMR, 112.5 115.3, 117.1, 118.5, 122.5, 123.2, 123.6, 125.5, 127.9, 128.4, 129.5, 135.6, 155.3, 158.4, 172.3; MS: *m/z*: 315 (M^+); Anal. calcd. for $C_{20}H_{13}NO_3$ (315.33): C, 76.18; H, 4.16; N, 4.44 %. Found: C, 76.07; H, 4.11; N, 4.35 %.

Ethyl 2-(1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1*H*)-yl)acetate (3)

A mixture of benzoxazinone **2** (0.01 mol) and ethyl glycinate (0.01 mol) in ethanol (20 mL) containing sodium acetate (0.01 mol) was heated under reflux for 3 hours. The reaction mixture was allowed to cool then poured into crushed ice. The precipitated solid was collected by filtration, dried and crystallized from ethanol.

Yellowish white crystals, yield: 69 %; m.p. 135-137 ^{o}C. IR spectrum (KBr, ν, cm^{-1}): 1609 (C=N), 1678, 1733 (2 CO), 2940, 2860 (CH_2); ^{1}H NMR (DMSO-d_6, δ ppm): 1.18 (t, 3H, CH_3), 3.83 (s, 2H, NCH_2), 4.32 (q, 2H ,CH_2), 7.15-7.63 (m, 9H, diphenylether-H), 7.90-8.36 (m, 4H, phthalazine-H); ^{13}C NMR, 14.7, 63.5, 65.3, 114.5, 115.2, 118.3, 118.5, 120.5, 121.2, 122.7, 123.5, 125.5, 126.3, 127.5, 128.3, 128.6, 135.5, 153.1, 168.5, 176.8; MS: *m/z*: 400 (M^+); Anal. calcd. for $C_{24}H_{20}N_2O_4$ (400.43): C, 71.99; H, 5.03; N, 7.00 %. Found: C, 71.86; H, 4.98; N, 6.82 %.

2-(1-Oxo-4-(4-phenoxyphenyl)phthalazin-2(1H)-yl)acetohydrazide (4)

An equimolar amount of ester **3** and hydrazine hydrate (0.01 mol) in ethanol (20 mL) was refluxed for 3 hours. The reaction mixture was allowed to cool and the precipitated solid was filtered, dried and crystallized from ethanol.

Yellow crystals, yield: 85 %; m.p. 233-235 ^{o}C. IR spectrum (KBr, ν, cm^{-1}): 1615 (C=N), 1670-1684 (2CO), 2937, 2900 (CH_2), 3447-3155 (NH_2, NH); ^{1}H NMR (DMSO-d_6, δ ppm): 3.36 (s, 2H, NCH_2), 7.13 (s, 2H ,NH_2, exchangeable), 7.11-7.71

(m, 9H, diphenylether-H), 7.78-8.35 (m, 4H, phthalazine-H), 12.80 (s, 1H, NH exchangeable); ^{13}C NMR, 65.5, 113.5, 114.8, 116.2, 118.7, 121.3, 123.5, 124.3, 127.5, 128.6, 128.9, 131.5, 133.5, 135.3, 153.5, 155.5, 169.5, 176.8; MS: *m/z*: 386 (M+); Anal. calcd. for $C_{22}H_{18}N_4O_3$ (386.41): C, 68.38; H, 4.70; N, 14.50 %. Found: C, 68.27; H, 4.55; N, 14.32 %

General procedure for synthesis of hydrazones 5a-c

Cerium (IV) ammonium nitrate (0.01 mol) was added to a mixture of hydrazide **4** (0.01 mol) and aromatic aldehydes (0.01 mol) namely benzaldehyde, 4-chlorobenzaldehyde and thiophene-2-carbaldehyde in ethanol (10 mL), the reaction mixture was stirred and heated under reflux for 1h. Water (5 mL) was added and the product solid was filtered, washed and recrystallized from proper solvent.

N-Benzylidene-2-(1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1H)-yl)acetohydrazide (5a)

Yellow powder, yield: 83 %; m.p. 215-217 ^{o}C. IR spectrum (KBr, ν, cm^{-1}): 1610 (C=N), 1680-1669 (2 CO), 2998, 2905 (CH_2), 3431 (NH); ^{1}H NMR (DMSO-d_6, δ ppm, 3.94 (s, 2H, NCH_2), 7.08-7.88 (m, 18H, diphenylether and benzylidene-H), 7.95-8.32 (m, 4H, phthalazine-H), 8.82 (s, 1H, CH=N), 12.82 (s, 1H, NH, exchangeable); ^{13}C NMR, 63.5, 114.5, 115.3, 116.3, 116.7, 117.5, 118.3, 120.5, 121.7, 123.2, 126.5, 128.3, 129.5, 133.4, 132.5, 133.1, 135.5, 145.3, 148.3, 1542.5, 155.5, 169.5, 177.4; MS: *m/z*: 474 (M+); Anal. calcd. for $C_{29}H_{22}N_4O_3$ (474.52): C, 73.40; H, 4.67; N, 11.81 %. Found: C, 73.27; H, 4.51; N, 11.68 %.

N-(4-Chlorobenzylidene)-2-(1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1H)-yl) acetohydrazide (5b)

Yellow powder, yield 84 %; m.p. 220-222 ^{o}C. IR spectrum (KBr, ν, cm^{-1}): 1620 (C=N), 1669-1677 (2 CO), 2903, 2980 (CH_2), 3437 (NH); ^{1}H NMR (DMSO-d_6, δ ppm): 3.74 (s, 2H, NCH_2), 7.12-7.69 (m, 13H, diphenylether and 4-chlorobenzylidene-H), 7.75-8.35 (m, 4H, phthalazine-H), 8.90 (s, 1H, CH=N), 12.81 (s, 1H, NH, exchangeable); ^{13}C NMR, 62.7, 118.1, 119.6, 121.5, 122.1, 123.3, 124.4, 125.4, 126.9, 127.3, 127.7, 128.1, 128.6, 130.3, 131.4, 134.4, 135.3, 136.1, 155.6, 156.7, 158.7, 163.1, 171,5; MS: *m/z*: 508 (M^+), 509 (M^{+1}); Anal. calcd. for

$C_{29}H_{21}ClN_4O_3$ (508.96): C, 68.44; H, 4.16; N, 11.01 %. Found: C, 68.28; H, 3.98; N, 10.87 %.

2-(1-Oxo-4-(4-phenoxyphenyl)phthalazin-2(1H)-yl)-N'-(thiophen-2-ylmethylene) acetohydrazide 5c

Yellow crystals, yield: 87 %; m.p. 214-216 ^{o}C. IR spectrum (KBr, ν, cm^{-1}): 1605 (C=N), 1678-1665 (CO), 2950, 2899 (CH_2), 3370 (NH); ^{1}H NMR (DMSO-d_6, δ ppm): 3.65 (s, 2H, NCH_2), 7.05-7.74 (m, 12H, diphenylether and 4-thiophene-H), 7.90-8.33 (m, 4H, phthalazine-H), 8.86 (s, 1H, CH=N), 11.74 (s, 1H, NH, exchangeable); ^{13}C NMR, 62.5, 113.2, 114.6, 115.5, 116.2, 118.1, 118.5, 119.5, 121.8, 122.5, 126.2, 128.3, 129.2, 129.6, 130.5, 131.5, 133.6, 135.2, 155.2, 167.5, 171.5 ; MS: *m/z*: 480 (M+); Anal. calcd. for $C_{27}H_{20}N_4O_3S$ (480.54): C, 67.49; H, 4.20; N, 11.66 %. Found: C, 67.41; H, 4.12; N, 11.53 %.

General procedures for the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles 6a-c

Method A: An equimolar amount of hydrazones **5a-c** (0.01 mol) and cerium (IV) ammonium nitrate (0.01 mol) was grinded together in mortar at room temperature for 30 min. Dichloromethane (10 mL) and water (10 mL) were added, then the organic phase was separated and dried over magnesium sulfate. After evaporation of solvent, the solid was collected and recrystallized from proper solvent to give oxadiazoles **6a-c**.

Method B: Cerium (IV) ammonium nitrate (0.01 mol) was added to a mixture of hydrazide **4** (0.01 mol), the same aromatic aldehydes (0.01 mol) in aqueous dichloromethane (20 mL), the whole reaction mixture was stirred and heated under reflux for 5 h. the progress of the reaction was monitored by TLC. Water (10 mL) was added and the organic phase was separated and dried over magnesium sulfate. After evaporation of solvent, the product solid was collected and recrystallized from proper solvent to give oxadiazoles **6a-c**.

4-(4-Phenoxyphenyl)-2-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl) phthalazin-1(*2H*) -one (6a)

Yellow powder, Yield: 77 %; m.p. 230-232 ^{o}C. IR (KBr, ν, cm^{-1}): 1610 (C=N), 1671 (CO), 2940, 2901 (CH_2); ^{1}H NMR (DMSO-d_6, δ ppm): 3.80 (s, 2H, NCH_2), 7.12-7.76 (m, 14H, diphenylether and benzylidene-H), 7.82-8.34 (m, 4H, phthalazine-H); ^{13}C

NMR, 59.5, 115.5, 117.3, 118.1, 119.3, 121.5, 122.3, 124.1, 126.1, 126.6, 127.9, 128.2, 129.0, 129.5, 130.2, 131.2, 131.7, 133.7, 145.9, 156.0, 157.5, 159.2, 173.7 ; MS: *m/z*: 472 (M^+); Anal. calcd. for $C_{29}H_{20}N_4O_3$ (472.50): C, 73.72; H, 4.27; N, 11.86 %. Found: C, 73.66; H, 4.16; N, 11.72 %.

2-((5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)-4-(4-phenoxyphenyl) phthalazin-1(*2H*)-one (6b)

Yellow powder, yield: 87 %; m.p. 240-242 ^oC. IR (KBr, ν, cm^{-1}): 1620 (C=N), 1677 (CO), 2901, 2880 (CH_2); ^1H NMR (DMSO-d_6, δ ppm): 3.60 (s, 2H, NCH_2), 7.12-7.76 (m, 13H, diphenylether and 4-chlorobenzylidene-H), 7.83-8.34 (m, 4H, phthalazine-H); ^{13}C NMR, 64.3, 116.5, 117.5, 118.3, 119.2, 122.2, 123.6, 126.4, 127.2, 128.6, 133.2, 135.3, 148.6, 150.5, 154.2, 155.2, 166.3; MS: *m/z*: 506 (M^+), 507 (M^{+1}); Anal. calcd. for $C_{29}H_{19}ClN_4O_3$ (506.95): C, 68.71; H, 3.78; N, 11.05 %. Found: C, 68.67; H, 3.69; N, 11.02 %.

4-(4-Phenoxyphenyl)-2-((5-(thiophen-2-yl)-1,3,4-oxadiazol-2-yl)methyl) phthalazin-1(2H)-one (6c)

Yellow powder, yield: 73 %; m.p.230-232 ^oC. IR (KBr, ν, cm^{-1}): 1618 (C=N), 1683 (CO), 2918, 2856 (CH_2); ^1H NMR (DMSO-d_6, δ ppm): 3.70 (s, 2H, NCH_2), 7.22-7.93 (m, 12H, diphenylether and thiophene-H), 7.75-8.34 (m, 4H, phthalazine-H); ^{13}C NMR, 62.5, 115.3, 117.2, 118.5, 120.5, 121.8, 122.5, 123.3, 126.1, 127.3, 128.5, 130.5, 133.2, 133.6, 135.5, 136.5, 148.6, 150.5, 154.2, 155.2, 166.3; MS: *m/z*: 478 (M^+); Anal. calcd. for $C_{27}H_{18}N_4O_3S$ (478.53): C, 67.77; H, 3.79; N, 11.71 %. Found: C, 67.65; H, 3.68; N, 11.64 %.

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