**Preparation and some reactions of a novel (*E*)-4-((1,3-diphenyl-1*H*-pyrazol-4-yl) methylene)-2-(4-nitrophenyl) oxazol-5(4*H*)-one containing 2,4-diphenyl pyrazole and investigation of their antimicrobial and anticancer activities**

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Abstract: New (*E*)-4-((1,3-diphenyl-1*H*-pyrazol-4-yl) methylene)-2-(4-nitrophenyl) oxazol-5(4*H*)-one (3) has been prepared by reaction of *p*-nitrohippuric acid (1) with 1,3-diphenyl-*1H*-pyrazol-4-carbaldehyde (2). Treatment of 3 with hydrazine hydrate gave the hydrazide derivative 4. Refluxing 4 with 6N HCl afforded the imidazolone derivative 5. Reaction of the hydrazide derivative 4 with benzoyl chloride yielded *N*-benzoyl derivative 6. Refluxing 6 with 6N HCl gave triazinone derivative 7. However, reaction of 6 with POCl3 yielded the oxadiazole derivative 8. Aminolysis of 3 with primary and /or secondary aliphatic amines gave the corresponding (*E*)-*N*-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-substitueted-3-oxoprp-1-en-2-yl)-4-nitrobenzamide (9a-d). On the other hand, refluxing 3 with aniline led to the formation of (*E*)-N-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-oxo-3-(phenylamino) pro-1-en-2-yl)-4-nitrobenzamide (10). Treatment of 3 with hydroxylamine hydrochloride in boiling pyridine yielded oxadiazinone derivative 11. The structures of synthesized compounds were elucidated on the basis of IR, 1HNMR, 13CNMR, MS data and elemental analysis. The prepared compounds were tested for antibacterial, antifungal and anticancer activity. The antimicrobial activities of the synthesized compounds have been studied against gram positive bacteria, gram negative bacteria and fungi by using agar well diffusion method which showed that compounds 3, 7 were the most effective gram positive. Compounds 3, 7 and 8 were effective against gram negative but less than gram positive*.* However,compounds 3, 4, 5, 6 were more effective against fungi. Furthermore, anticancer activities of some selected compounds were tested against human hepatocellular (HepG2) cancer cell line. Compound 6 showed moderate cancer cell growth inhibition. Also, the anticancer activities against Ascitic Carcinoma showed that compounds 6 showed the highest antitumor effects.

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1. Introduction

The importance and diverse biological activities of each of oxazolone and pyrazole derivatives prompted us to report the synthesis of some new heterocycle-based chromophores based on oxazolone and pyrazole cores. Therefore, the present study will focus on the coupling of two excellent molecular moieties, oxazole and pyrazole. This combination was suggested in an attempt to investigate the influence of this new structure on the anticipated biological activities, hoping to add some synergistic biological significance to the target molecule. Also, we will study the behaviour of the new compound towards different nucleophile species in order to achieve heterocyclic. Oxazolone provides a basic skeleton structure and also is a part of great importance for its drug characteristics. These compounds exhibit important biological activities such as antimicrobial [1], antibacterial [2], analgesic [3], antifungal [4], antitumor [5,6], anti-inflammatory [7], neuroleptic [8], sedative [9], antidiabetic [10]and antiobesity [11]. Also, pyrazole and its derivatives constitutes an important class of heterocyclic compounds and has received widespread attention due to their diverse pharmacological activites such as anti-inflammatory analgesic [12,13,14] antimicrobial [15,10] anticancer [18,19] antihypertensive [20,21] antidiabetic [22,23] antidepressant-anticonvulsant [24,25] etc. There are numerous pyrazole containing drugs approved by United States Food and Drug Administration for appropriate.

2. Results and Discussion

In the present work, new (*E*)-4-((1,3-diphenyl-1*H*-pyrazol-4-yl) methylene)-2-(4-nitrophenyl)oxazol-5(4*H*)-one **(3)** has been synthesized by two different methods. In the first (Method A) by the reaction of *p*-nitrohippuric acid **(1)** with 1,3-diphenyl-1*H*-pyrazol-4-carbaldehyde **(2)** in the presence of sodium acetate as a basic catalyst and acetic anhydride as dehydrating agent according to Perkin-Erlenmeyer's reaction conditions [24-28]. (Method A) High temperature is required, low yield and separation is crucial. Recently, the second (Method B) which is green method for high yield, short reaction time, more efficient and easy work up uses L-proline as organic catalyst which is easily available and inexpensive instead of sodium acetate.

The reactions may proceed by the following mechanism:



**Scheme 1**



**Scheme 2**

The structure of **3** was supported by correct analytical and spectral data. IR showed absorption band at 1795 cm-1 due to C=O (Oxazolone). Mass spectrum revealed the correct ion peak at *m/e* 436. **13**CNMR exhibited peak at 165.92 due to C=O (Oxazolone). The special arrangement of compound **3** was found to be *E*-isomer based on the assumption that the vinylic proton appears at higher ẟ value (7.26) because it is more deshielded than the *Z*-isomer which appears at less ẟ value.

In the present study, we intend to investigate the nucleophilic reaction of hydrazine hydrate with the oxazolone derivative **3** in refluxing benzene [25] to give the hydrazide derivative (*E*)-*N*-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-hydrazineyl-3-oxoprop-1-en-2-yl)-4-nitrobenzamide **(4)**.

The structure of compound **4** was confirmed by correct analytical data, IRshowed absorption bands due to NH and C=O groups and **1**HNMR spectrum revealed signals due to 2 NH, NH**2**, vinylic and aromatic protons. **13**CNMR exhibited peaks at 163.87, 164.23 due to NH-CO and NH-CO-Ph respectively. Also, another support from mass spectrum which showed the correct molecular ion peaks in addition to some of the abundant peaks (cf. experimental).The assignment for structure of compound **4** is based on the fact that the vinylic proton of *E*-isomer is more deshielded by phenyl and *p*-nitrobenzoyl groups if compared with the Z-isomer.

The present study aimed to utilize the *E*-isomer of the hydrazide derivative to prepare some important biologically active heterocyclic compounds. Thus, refluxing the hydrazide derivative **4** with 6N hydrochloric acid led to the formation of **5** which may possess one of two possible structures, the imidazolone derivative **5** or the trizinone derivaive **5⸌.**

The structure of the two products **5**, **5⸌** was confirmed by their spectroscopic properties. IR spectrum exhibited absorption bands at: 3353, 3279 cm-1, 1712 cm-1 due to NH**2** and C=O respectively. The presence of absorption band of C=O at higher frequency (larger than 1700) establish the existence of the product as imidazolone derivative, (*E*)-3-amino-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-(4-nitrophenyl)-3,5-dihydro-4*H*-imidazol-4-one **(5).**

**1**HNMR spectrum of **5** support the proposed structure as it revealed one singlet at 5.44 (s, 2H, NH**2**exchangeable) and not two singlet signals for 2 NH protons in the downfield region for **5⸌.** Also, **13**CNMR revealed peak at 169.06 due to CO-imidazolyl.

On the other hand, treatment of compound **4** with benzoyl chloride in boiling benzene gave (*E*)-*N*-(3-(2-benzoylhydrazineyl)-1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-en-2-yl)-4-nitrobenzamide **(6).** Structure of **6** was confirmed by IR spectrum which showed absorption bands at 3261 cm-1and 1665,1646,1620 cm-1 due to 3 NH and 3 C=O groups. **1**HNMR spectrum revealed a singlet signal for vinyl proton and three singlets due to three NH protons. **13**CNMR showed three peaks at 164.32, 165.63, 169.09 due to NH-CO-Ph, C=C-CO-NH, NH-CO-PhNO**2** respectively. The configuration of compound **6** as (*E*)-isomer is based on the higher value for vinylic proton signal and to minimize the steric hindrance due to benzoylation. Also, mass spectrum exhibited the correct molecular ion peak.

Refluxing compound **6** with 6N hydrochloric acid gave (*E*)-2-benzoyl-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-(4-nitrophenyl)-2,5-dihydro-1,2,4-triazin-6(1*H*)-one **(7).** The structure of compound **7** was supported by IR spectrum which revealed absorption bands at 3200 cm-1 and 1657, 1620 cm-1 due to NH and 2 C=O groups. The value for C=O absorption is a good support for the presence of triazinone structure. **13**CNMR exhibited peaks at 165.65, 169.10 due to NH-CO and N-CO respectively. Also, mass spectrum showed the correct ion peak for compound **7**. The chemical proof for the proposed structure was established by its conversion to compound **6** by boiling with **10** % NaOH.

However, the reaction of compound **4** with POCl**3** yielded (*E*)-*N*-(2-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1-(5-(4-nitrophenyl)-1,3,4-ox- adiazol-2-yl)vinyl)benzamide **(8).** Thestructure of **8** was confirmed by IR spectrum which exhibited absorption bands at 3200 cm-1 and 1662 cm-1 due to NH and C=O. **13**CNMR revealed peak at 163.38 due to CO-NH. Also, mass spectrum and NMR supported the proposed structure.

Aminolysis of compound **3** with primary and/or secondary amines namely, ethylamine, diethylamine, morpholine and/or piperidine in boiling benzene [27, 28, 29] gave the corresponding (*E*)-*N*-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-substitueted-3-oxoprop-1-en-2-yl)-4-nitrobenzamide **(9a-d).**The structer of **9a-d** can be deduced from their spectroscopic properties. The IR spectrum revealed bands due to C=O at lower frequency values and the presence of NH band which support the opening of the oxazolone ring by nucleophilic attack of amines. Furthermore,**1**HNMR spectrum showed one singlet signal in the downfield region due to the CO-NH protons. Also, **13**CNMR exhibited two peaks for two CO in the correct position (cf. experimental).

However, refluxing of **3** with aniline in EtOH: DMF (1:2) led to the formation of (*E*)-*N*-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-oxo-3-(phenylamino)prop-1-en-2-yl)-4-nitrobenzamide **(10).** The proposed structure was confirmed by correct analytical data. IR spectrum which exhibited absorption bands at 3268 cm-1 and 1658, 1626 cm-1 due to NH and 2 C=O.**13**CNMR revealed two peaks at 163.54, 164.27 due to Ph-CO-NH and Ph-NH-CO respectively. Also, mass spectrum showed the correct ion peak for compound **10**.

On the other hand, when compound **3** was submitted to react with hydroxylamine hydrochloride in boiling pyridine, the corresponding (*E*)-4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-6-(4-nitrophenyl)-2*H*-1,2,5-oxadiazin-3(4*H*)-one **(11)** was obtined.

The IR spectrum showed bands at 3202 cm-1 and at 1691 cm-1 due to NH and C=O. The lower frequency value of C=O group confirmed the six membered oxadiazine structure. **13**CNMR exhibited a peak at 165.16 due to CO- which confirm structure **11**.



**Scheme 3**



**Scheme 4**

**3. Biological Study**

**3.1 Antimicrobial activity**

The results clarified that the different compounds used in the study exhibited a varying degree of antimicrobial activity against all microorganisms tested (Table 1)The gram-positive bacteria showed the maximum zone of inhibition (16-20 mm) with the compounds **3, 7.** It was observed that compounds **3, 7** were the most effective against *S.aureus* with zone of inhibition 20 mm, 16 mm respectively. Whereas, *S. dermatitis* was more affected by compound **7** and the inhibition zone was 14 mm. The gram-negative bacteria were less affected by the tested compounds, where zone of inhibition was varied between 13 mm and 14 mm with the compounds **3**, **7** and **8** against *E.coli.* However,tested compounds were more effective against fungi. The highest zone of inhibition against *C.albicans* were ranged between **15** mm and **17** mm with the compounds **3, 4.** The maximum inhibition zone (22 mm and 21mm) was observed with the compounds **6** against *T.rubrum.* The results suggested that the tested compounds were more effective against *T.rubrum, S.aureus, S.dermatitis,* and finally *E.coli.* Positive control Streptomycin (30 µg) gave corresponding zones of inhibition ranged between 25 mm and 28 mm against tested species.

**Table 1. Antimicrobial activity of different prepared compounds (20 mg/ml) against gram positive bacteria (*Staphylococcus aureous* PC1219, *Staphylococcus epdermatitis*), gram negative bacteria (*Escherichia coli* NCIM2065, *Klebseilla* sp.), and fungi (*Candida albicans, Trycophyton rubrum*).**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Chemical No.** | **Zone of inhibition (mm)** | | | | | |
| **Gram positive** | | **Gram negative** | | **Fungi** | |
| ***S.aureus*** | ***S. dermatitis*** | ***E. coli*** | ***K.* sp*.*** | ***C. albicans*** | ***T. rubrum*** |
| **3** | 20±1.4 | 12±0.8 | 13±1.3 | 11±0.3 | 17±0.8 | 08±0.5 |
| **4** | 08±0.6 | 07±0.3 | 09±0.5 | 08±0.6 | 16±0.9 | 08±0.7 |
| **5** | N | N | N | N | 14±0.6 | 11±0.8 |
| **6** | 12±0.6 | 10±0.7 | 12±0.7 | 10±0.6 | 12±0.9 | 22±1.6 |
| **7** | 16±1.1 | 14±0.9 | 14±0.6 | 12±0.8 | 11±0.6 | 06±0.4 |
| **8** | N | N | 13±1.0 | 10±0.4 | 10±0.4 | 06 ±0.2 |
| **9a** | N | N | 09±0.2 | 09±0.5 | 12±0.5 | 09±0.3 |
| **9b** | N | N | 10±0.4 | 08±0.6 | 08±0.4 | 12±0.5 |
| **9c** | N | N | 09±0.9 | 10±0.3 | 09±0.4 | 10±0.7 |
| **9d** | 07±0.3 | 10±0.5 | 09±0.4 | 10±0.4 | 10±0.3 | 09±0.6 |
| **10** | N | N | N | N | 11±0.8 | 08±0.4 |
| **11** | N | N | N | N | 07±0.3 | 07±0.3 |
| **Positive control** | 25±2.1 | 26±2.0 | 28±2.4 | 26±2.7 | 25±2.4 | 27±2.5 |
| **Positive control** | 25±2.1 | 26±2.0 | 28±2.4 | 26±2.7 | 25±2.4 | 27±2.5 |

N: Negative effect, Positive control: Streptomycin (30 µg) for bacteria and Amphotericin B (100 μg) for fungi.

**3.2 Anti cancer activity**

**3.2.1 *In vitro* anticancer activity of the prepared compounds**

The cytotoxicity of the prepared compounds was evaluated *in vitro* against the human hepatocellular (HepG2) cancer cell lines by using MTT testing. As compared with the cytotoxicity of cisplatin, which is the most promising anticancer drug for the treatment and prevention of hepatic cancer cells that was evaluated under the same conditions. The results of inhibition concentration that killed 50 % of cells (IC50) of cisplatin and the tested compounds are shown in (Table 2.) The results showed that the tested compounds exhibited some hepatocellular-growth inhibiting effects after 24 hours of *in vitro* treatments as the following: **3, 6, 7,** and **9c** after 24 hours of treatments *in vitro* was 88.24, 179.68, 247.45, 287.93 µg/ml, respectively. **6** showed moderate inhibitory effect, with an IC50 value of 88.24 μg/ml.

**Table 2. *In vitro* cytotoxicity of compounds against HepG2 cancer cell lines that showed IC50 values of cisplatin and the tested compounds**

|  |  |
| --- | --- |
| **Compound** | **IC50 (μg/ml)** |
| **Cisplatin** | **31.14** |
| **3** | 287.93 |
| **6** | 88.24 |
| **7** | 179.68 |
| **9c** | 247.45 |

**3.2.2Anticancer profiling in the different group of mice upon treatments**

As compared to the EAC–bearing mice (control group), the results showed that the treatment with cisplatin (2 mg/kg/6consecutive days) daily after one day of tumor inoculation led to a significant decrease in total volume and total number of anticancer cells., the treatment with **6** showed the highest antitumor effects when compared with the control group (Table 3).

**Table 3. Total Ehrlich Ascitic Carcinoma (EAC) volume, count and viability of the different groups of tumor-bearing mice.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Compounds** | **Total volume (ml)** | **Total count (×106/mouse)** | **Viable cells (×106/mouse)** | **Dead cells**  **(×106/mouse)** |
| **EAC-control** | **13 ± 1.3** | **610 ± 7.8** | **603 ± 7.17** | **7 ± 0.9** |
| **Cisplatin (reference drug)** | **0.8 ± 0.23** | **52 ± 1.02** | **9 ± 0.98** | **43 ± 3.9** |
| **3** | 10.5 ± 3.12 | 457 ± 3.98 | 444 ± 3.87 | 13 ± 1.22 |
| **6** | 2.2 ± 0.43 | 92 ± 1.34 | 45 ± 1.86 | 47 ± 2.03 |
| **7** | 8.3 ± 1.65 | 352 ± 2.57 | 320 ± 1.98 | 32 ± 0.76 |
| **9c** | 8.9 ± 2.56 | 362 ± 3.05 | 323 ± 2.59 | 29 ± 1.15 |

4. Conclusion

A series of novel oxazolones, hydrazide, triazine, oxadiazole and *N*-benzoyl derivatives were prepared and assayed in a variety of biological tests for antibacterial, antifungal and anticancer activity. It is showed that compounds 3, 7, 8 were the most effective against antibacterial. However, compounds 3, 4, 6 were more effective against fungi. Furthermore, compound 6 tested against human hepatocellular and showed moderate cancer cell growth inhibition futherwise, the highest antitumor effects observed for compound 6 against Ascitic Carcinoma.

**5. Experimental**

All purchased solvents and chemicals were of analytical grade and used without further purification. All melting points were determined using open capillaries on a Büchi melting point B-540 apparatus and are uncorrected. Infrared spectra were recorded on a PerkinElmer spectrum 100 FTIR spectrometer. 1H and 13C NMR spectra were recorded on (JNM-ECA 500 MHz) made by jeol Japan at Mansoura University using DMSO-*d6* as a solvent, and TMS as an internal standard; the chemical shifts are given in δ units (ppm). Abbreviations used for NMR signals: *s* = singlet, *d* = doublet, *t* = triplet, and *m* = multiplet. Mass spectra were performed on a Shimadzu mass spectrometer at 70 eV. The mass spectra were recorded on a Shimadzu GC-MS QP-2010 plus mass spectrometer operating at 70eV at the Micro Analytical Center of Cairo University. Microanalysis were performed at Microanalysis Center, Cairo University, Cairo, Egypt.

**Synthesis of** **(*E*)-4-((1,3-diphenyl-1H-pyrazol-4-yl) methylene)-2-(3-nitrophenyl) oxazol-5(4H)-one (3)**

**Method** **A:** A mixture of *p*-nitrohippuric acid **(1)** (2.24 g, 0.01 mol) and 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **(2)** (2.48 g, 0.01 mol) in glacial acetic acid (10 mL), acetic anhydride (15 mL) and freshly fused sodium acetate (0.82 g, 0.01 mol) was heated on a steam bath for 6 h. The reaction mixture was allowed to cool down at room temperature. Then, ice cold water (50 mL) was added to the reaction mixture. The solid product obtained was filtered off and crystallized from EtOH to affordcompound **3.**

**Method B:** (L*-*proline). A mixture of *p*-nitrohippuric acid **(1)** (0.45 g, 0.002 mol) and 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **(2)** (0.50 g, 0.002 mol) was heated under reflux in acetic anhydride (2 mL) containing  L-proline (0.023 g, 0.0002 mol) for 40 minutes at 80°C. The solid obtained after cooling at room temperature was filtered off, washed with water several times and recrystallized from EtOH to give compound **3**.

**(*E*)-4-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-2-(3-nitrophenyl)oxa- zol-5(4H)-one (3)**

Orange powder, mp 279 - 280°C.

Yield, A= 37%, B= 85%.

**IR** (νmax, cm-1): 3074 (CH arom.), 1795 (CO oxazolone), 1647 (C=C), 752, 694 (monosubstituted benzene), 855 (*p*-disubstituted benzene).

**1HNMR (DMSO-d6)**: δH (ppm): 7.24 (s, 1H, CH=), 7.43 ــ 7.51 (m, 1H, Ar-H), 7.56 – 7.63(m, 5H, Ar-H), 7.72 (d, 2H, *J* = *7.5* *Hz*, Ar-H), 8.07 (d, 2H, *J* = *7.5* *Hz,* Ar-H), 8.42 (d, 2H, *J* = *9 Hz,* Ar-H), 8.50 (d, 2H, *J* = *9* *Hz,* Ar-H), 9.38 (s, 1H, pyrazolyl).

**13CNMR (DMSO-d6):** 115.35 (CH=), 119.74 (C4-pyrazolyl), 130.85 (C5-pyrazolyl), 138.70 (C4-oxazolone), (123.91, 124.27, 127.40, 127.88, 128.80, 129.10, 129.27, 129.50, 129.78, 131.09, 131.87, 149.94) (Ar-C), 154.52 (C3-pyrazolyl), 160.11 (C2-oxazolone), 165.92 (CO-oxazolone).

**MS: *m/z* (%):** 437 (M+ +1, 12.9), 436 (M+,46.03), 258 (70.31), 231 (12.06), 150 (40.92), 104 (75.69), 77 (100).

**Anal. Calcd for C25H16N4O4 (436.43) =** C, 68.80; H, 3.70; N, 12.84 %.

**Found =** C, 68.70; H, 3.45; N, 12.86 %.

**Synthesis of (*E*)-*N*-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-hydrazineyl-3-oxoprop-1-en-2-yl)-4-nitrobenzamide (4)**

A mixture of compound **3 (**4.36 g, 0.01 mol) in benzene (50 mL) was treated with hydrazine hydrate (1.00 g, 0.02 mol) and heated under refluxed for 3 h, after cooling. The solid that separated out was filtered, dried and recrystallized from MeOH to give pall yellow powder **4.**

Pale yellow powder, mp 223 - 225°C.

Yield = 94%.

**IR** (νmax, cm-1): 3403, 3318, 3268 (NH2, NH), 1663,1641 (2CO amides), 1598 (C=C), 752,703 (monosubstituted benzene), 850 (*p*-disubstituted benzene).

**1HNMR (DMSO-d6**: δH (ppm): 4.40 (br.s, 2H, NH2 exchangeable), 7.14 (s, 1H, CH=), 7.31 (t, 1H, *J* = *6.5* *Hz*, Ar-H), 7.46 - 7.53 (m, 5H, Ar-H), 7.65 (d,2H, *J* = *7.5* *Hz*, Ar-H), 7.71 (d, 2H, *J* *= 7.5* *Hz*, Ar-H), 8.24 (d, 2H, *J* *= 8.5* *Hz*, Ar-H), 8.36 (d, 2H, *J* = *8 Hz*, Ar-H), 8.61 (s, 1H, pyrazolyl), 9.60 (br. s, 1H, NH-CO, exchangeable), 10.12 (br.s, 1H, NH-CO-Ph, exchangeable)**.**

**13CNMR (DMSO-d6)** δ = 114.78 (C4-pyrazolyl), 123.31 (CH=), 129.49 (C5-pyrazlyl), 132.20 (CH=C), 149.15 (C3-pyrazolyl), (118.64, 119.59, 126.94, 128.05, 128.30, 128.36, 128.53, 128.78, 129.73, 139.05, 139.65, 152.40) (Ar-C), 163.87 (NH-CO), 164.23 (NH-CO-Ph).

**MS: *m/z* (%) =** 469 (M++1, 0.1), 468 (M+, 0.29), 450 (100), 436 (57.12), 258 (30.05), 150 (7.65), 104 (13.48), 77 (26.88).

**Anal. Calcd for C25H20N6O4 (468.47) =** C, 64.10; H, 4.30; N, 17.94 %.

**Found =** C, 64.33; H, 4.41; N, 17.86 %.

**Synthesis of (*E*)-3-amino-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene) -2-(4-nitrophenyl)-3,5-dihydro-4*H*-imidazol-4-one (5)**

A mixture of of compound **4** (4.68 g, 0.01mol) and (10 mL) 6NHCl was heated under reflux for 2 h, after cooling. The solid that separated out was crystallized from EtOH to afford compound **5**.

Fluffy orange, mp 293 - 295°C

Yield = 77%.

**IR** (νmax, cm-1): 3353, 3279 (NH2), 1712 (CO), 1612 (C=C), 759, 697 (monosubstituted benzene), 859 (*p*-disubstituted benzene).

**1HNMR (DMSO-d6)**: δH (ppm): 5.44 (s, 2H, NH2 exchangeable), 7.14 (s, 1H, CH=), 7.42 (t, 1H, *J = 7.5 Hz*, Ar-H), 7.57 – 7.60 (m, 5H, Ar-H), 7.70 (d, 2H, *J = 8.5 Hz*, Ar-H), 7.98 (d, 2H, *J = 7.5 Hz*, Ar-H), 8.38 (d, 2H, *J = 9.5 Hz*, Ar-H), 8.72 (d, 2H*, J = 9 Hz*, Ar-H), 9.33 (s, 1H, pyrazolyl).

**13CNMR (DMSO-d6)** δ **=** 115.64 (CH=), 119.50 (C4-pyrazolyl), 129.78 (C5-pyrazolyl), 135.67 (C5-imidazolyl), 148.84 (C2-imidazolyl), (119.65, 123.34, 126.40, 127.61, 128.74, 129.04, 130.93, 131.53, 131.63, 134.30, 138.83, 154.30) (Ar-C), 157.80 (C3-pyrazolyl), 169.06 (CO-imidazolyl).

**MS: *m/z* (%) =** 451 (M+ +1, 29.68), 450 (M+, 100), 434 (15.08), 164 (32.72), 118 (44.12), 104 (11.19), 77 (45.41).

**Anal. Calcd for C25H18N6O3 (450.46) =** C, 66.66; H, 4.03; N, 18.66%.

**Found =** C, 66.50; H, 4.11; N, 18.86 %.

**Synthesis of (*E*)-*N*-(3-(2-benzoylhydrazineyl)-1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-en-2-yl)-4-nitrobenzamide (6)**

Benzoyl chloride (1.40 g, 0.01mol) was added to solution of **4** (4.68 g, 0.01 mol) in (20 mL) dry benzene. The reaction mixture was heated under reflux at 80°C for 3 h, the solvent was distilled off under reduced pressure and the residue was poured into ice-cold water. The solid separated was filtered off, washed with water and recrystallized from MeOH to give compound **6.**

Yellow powder, mp 189 - 190°C.

Yield = 84%.

**IR** (νmax, cm-1): 3261 (NH), 1665, 1646, 1620 (3CO amide), 1600 (C=C), 756, 685 (monosubstituted benzene), 853 (*p*-disubstituted benzene).

**1HNMR (DMSO-d6)**: δH (ppm): 7.18 (s,1H, CH=), 7.35 (t, 1H, *J = 6.5 Hz*, Ar-H), 7.48 - 7.53 (m, 6H, Ar-H), 7.65 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H), 7.75 (t, 2H, *J = 7.5 Hz,* Ar-H), 7.89 (d,2H*, J = 8 Hz*, Ar-H), 8.26 (t, 2H, *J = 9 Hz,* Ar-H), 8.37 (d, 2H, *J = 9 Hz,* Ar-H), 8.71 (s,1H pyrazolyl), 10.29 - 10.58 (3s, 3H, NH).

**13CNMR (DMSO-d6) δ =** 114.04 (C4-pyrazolyl), 123.37 (CH=), 130.96 (C5-pyrazolyl), 134.33 (CH=C), 149.21(C3-pyrazolyl), (118.74, 119.54, 127.49, 128.36, 128.46, 128.76, 128.83, 128.88, 129.07, 129.54, 129.79, 132.14, 135.70, 139.04, 139.56, 152.60) (Ar-C), 164.32(NH-CO-Ph),165.63 (C=C-CO-NH), 169.09 (NH-CO-PhNO2).

**MS: *m/z* (%):** 573 (M++1, 0.73), 572 (M+, 1.42), 450 (27.43), 436 (40.66), 258 (58.57), 231 (12.59), 150 (23.35), 105 (40.47), 104 (39.05), 77 (100), 76 (38.47).

**Anal. Calcd for C32H24N6O5 (572.58) =** C, 67.13; H, 4.23; N, 14.68 %.

**Found =** C, 67.40; H, 4.03; N, 14.78 %.

**Synthesis of (*E*)-2-benzoyl-5-((1,3-diphenyl-1*H*-pyrazol-4-yl) methylene)-3-(4-nitrophenyl)-2,5-dihydro-1,2,4-triazin-6(1*H*)-one (7)**

A mixture of compound **6** (5.72 g, 0.01 mol) and 6N HCl (10 mL) was heated under reflux for 2 h, left to cool. The solid obtained was filtered off, washed with H2O and recrystallized from MeOH to yield compound **(7)**.

Orange powder, mp 229 - 231°C.

Yield = 81%.

**IR** (νmax, cm-1): 3200 (NH), 1657, 1620 (2CO amides), 1600 (C=C), 755, 699 (monosubstituted benzene), 853 (*p*-disubstituted benzene).

**1HNMR (DMSO-d6)**: δH (ppm): 7.15 (s, 1H, CH=), 7.33 (t, 2H, *J = 6 Hz*, Ar-H), 7.49 – 7.52 (m, 5H, Ar-H), 7.68 – 7.75 (m, 4H, Ar-H), 7.90 (d, 2H, *J = 7.5 Hz,* Ar-H), 7.99 (d, 2H, *J = 7.5 Hz,* Ar-H), 8.27 (d, 2H, *J =8.5 Hz,* Ar-H), 8.38 (d, 2H, *J =8.5 Hz,* Ar-H) 8.68 (s, 1H pyrazolyl), 10.48 (s, 1H, NH).

**13CNMR (DMSO-d6) δ =** 114.64 (CH=),115.67 (C4-pyrazolyl), 129.80 (C5-pyrazolyl), 139.05 (C5-triazine), (118.75, 119.54, 123.39, 127.50, 128.37, 128.48, 128.65, 128.77, 128.84, 129.07, 129.53, 138.86, 148.88, 149.22, 152.62, 154.35) Ar-C, 164.15 (C3-pyrazolyl), 164.35 (C3-triazine), 165.65 (NH-CO), 169.10 (N-CO).

**MS: *m/z* (%) =** 555 (M++1, 3.37), 554 (M+, 9.30), 437 (4.88), 436 (28.88),259 (7.61), 258 (34.51), 231 (5.66), 150 (16.10), 105 (57.54), 104 (34.85), 77 (100), 76 (25)**.**

**Anal. Calcd for C32H24N6O5 (554.57) =** C, 69.31; H, 4.00; N, 15.15 %.

**Found =** C, 69.50; H, 4.20; N, 15.40 %.

**Synthesis of (*E*)-*N*-(2-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) vinyl) benzamide (8)**

phosphorus oxychloride (10 mL) was added dropwise to compound **6** (0.92 g, 0.0016 mol). The reaction mixture was refluxed for 2 h at 100°C, then left to cool. The solid obtained after pouring into ice-cold water was filtered off and recrystallized from EtOH to afford compound **8**.

Red crystal, mp 200 - 202°C.

Yield = 60.21 %.

**IR** (νmax, cm-1): 3200 (NH), 1662 (CO), 1600 (C=C), 754,688 (monosubstituted benzene), 833 (*p*-disubstituted benzene).

**1HNMR (DMSO-d6)**: δH (ppm): δH= 7.25 (s, 1H, CH=), 7.45 – 7.71 (m, 9H, Ar-H), 7.90 -8.03 (m, 5H, Ar-H), 8.37- 8.59 (m, 5H, Ar-H), 8.73 (s, 1H, pyrazolyl), 9.46 (s, 1H, NH).

**MS: *m/z* (%) =** 555 (M++1, 6.63), 554 (M+, 17.90), 435 (3.51), 243 (1.15), 231(1.71), 128 (1.21), 105 (100), 104 (8.40), 77 (60.06), 76 (7.64).

**Anal. Calcd for C32H22N6O4 (554.57) =** C, 69.31; H, 4.00; N, 15.15 %.

**Found =** C, 69.21; H, 4.20; N, 15.35 %.

**General procedure for the synthesis of (*E*)-*N*-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-substitueted-3-oxoprop-1-en-2-yl)-4-nitrobenzamide (9a-d)**

A mixture of **3** (4.36 g, 0.01 mol) in dry benzene (50 mL) was treated with primary and/or secondary amines namely, ethylamine, diethyl amine, morpholine and/or piperidine (0.01mol) was heated under refluxed for 6 h, the solid products that separated after cooling and evaporation of excess solvent under reduced pressure were filtered off and recrystallized from a suitable solvent to yield **9a-d**.

**Synthesis of (*E*)-*N*-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-(ethylamino)-3-oxoprop-1-en-2-yl)-4-nitrobenzamide (9a)**

Bright yellow, mp 202 - 204°C.

Yield = 87%.

**IR** (νmax, cm-1): 3339 (NH), 3051 (CH, aromatic), 2920, 2890 (CH, aliphatic) 1660,1646 (2CO amides), 1621 (C=C), 749, 696 (monosubstituted benzene), 850 (*p*-disubstituted benzene).

**1HNMR (DMSO-d6)**: δH (ppm): 1.04 (t, 3H, *J=7.5 Hz*, CH3), 3.16 (q, 2H, *J=7.5 Hz*, CH2), 7.19 (s, 1H, CH=) 7.32 (t, 1H, *J = 7 Hz,* Ar-H), 7.45 – 7.52 (m, 5H, Ar-H), 7.64 (d, 2H, *J = 8 Hz,* Ar-H), 7.70 (d, 2H, *J = 7.5 Hz,* Ar-H), 8.19 ــ 8.25 (m, 3H, 2Ar-H + 1H, pyrazolyl), 8.36 (d, 2H, *J = 9 Hz,* Ar-H), 8.57 (s, 1H, NH-ethyl), 10.12 (s, 1H, NH-CO).

**13CNMR (DMSO-d6):** δ= 14.84 (CH3- aliphatic), 33.99 (CH2- aliphatic), 114.91 (C4-pyrazolyl), 123.40 (CH=), 129.77 (C5-pyrazolyl), 132.23 (CH=C), 149.20 (C3 -pyrazolyl), (118.64, 119.68, 126.97, 127.99,128.29, 128.55, 128.80, 129.49, 129.55, 139.05, 139.07, 152.41) (Ar-C), 164.004 (CO-NH-ethyl), 164.10 (CO-NH).

**MS: *m/z* (%) =** 482 (M++1, 1.76), 481 (M+, 4.13), 464 (20.09), 463 (57.32),462 (19.83), 437 (18.85), 436 (57.39), 315 (6.59), 271 (4.98), 259 (27.85), 258 (100), 231 (14.84), 150 (43.35), 149 (21.44), 104 (59.39), 103 (29.53), 92 (16.95), 77 (56.89), 76 (26.26)**.**

**Anal. Calcd for C27H23N5O4 (481.51) =** C, 67.35; H, 4.81; N, 14.54 %.

**Found =** C, 67.20; H, 4.61; N, 14.66 %.

**Synthesis of (*E*)-*N*-(3-(diethylamino)-1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-en-2-yl)-4-nitrobenzamide (9b)**

Yellow powder, mp 225 - 228°C.

Yield = 70%.

**IR** (νmax, cm-1): 3184 (NH), 2934, 2920 (CH, aliphatic), 1674, 1597 (2CO amides), 1542 (C=C), 746,700 (monosubstituted benzene), 851 (*p*-disubstituted benzene).

**1HNMR (DMSO-d6)**: δH (ppm): 1.07 (t, 6H, J= 7 Hz, 2CH3), 3.55 (q, 4H, 2CH2), 6.19 (s, 1H, CH=), 7.32 – 7.40 (m, 2H, Ar-H), 7.46 (t, 2H, *J = 7.5 Hz,* Ar-H), 7.52 (t, 2H, *J = 7.5 Hz,* Ar-H), 7.62 (d, 2H, *J = 7.5 Hz,* Ar-H), 7.87 (d, 2H, *J = 7.5 Hz,* Ar-H), 8.11 (d, 2H, *J = 9 Hz,* Ar-H), 8.31 (d, 2H, *J = 8.5 Hz,* Ar-H), 8.85 (s, 1H, pyrazolyl), 10.29 (s.1H, NH-CO).

**13CNMR (DMSO-d6) δ =** 12.31 (CH3-aliphatic), 42.81 (CH2-aliphatic), 114.50 (C4-pyrazolyl), 123.40 (CH=), 130.43 (C5-pyrazolyl), 132.54 (CH=C), (111.92, 118.63, 126.71, 127.10, 128.40, 128.62, 128.68, 129.42, 129.69, 138.91, 139.27, 151.56) (Ar-C), 149.20 (C3-pyrazolyl), 163.78 (CO-NH), 167.31 (CO-N).

**MS: *m/z* (%)** = 510 (M+ +1, 0.50), 509 (M+, 1.44), 438 (5.36), 437 (30.34), 436 (100.0), 259 (13.63), 258 (60.15), 231 (9.31), 155 (3.93), 150 (20.40), 104 (27.20), 103 (3.06), 101 (3.09), 77 (32.04), 76 (15.55), 75 (4.79).

**Anal. Calcd for C29H27N5O4 (509.57) =** C, 68.36; H, 5.34; N, 13.74 %.

**Found =** C, 68.20; H, 5.20; N, 13.86 %.

**Synthesis of (*E*)-*N*-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-morpholino-3-oxoprop-1-en-2-yl)-4-nitrobenzamide (9c)**

Pale yellow, mp 267 - 269°C

Yield = 91%.

**IR** (νmax, cm-1): 3123 (NH), 2940, 2856 (CH-aliphatic), 1674,1600 (2CO amides), 1548 (C=C), 742,699 (monosubstituted benzene), 850 (*p*-disubstituted benzene)**.**

**1H NMR (DMSO-d6)**: δH (ppm): 3.63 (s, 8H, morpholine ring), 6.25 (s, 1H, CH=), 7.33 (t, 1H, *J = 7.5 Hz,* Ar-H), 7.40 (t, 1H, *J = 7.5 Hz,* Ar-H), 7.47 – 7.53 (m, 4H, Ar-H), 7.63 (d, 2H, *J = 7.5 Hz,* Ar-H), 7.87 (d, 2H, *J = 7.5 Hz,* Ar-H), 8.15 (d, 2H, *J = 9 Hz,* Ar-H), 8.32 (d, 2H, *J = 9 Hz,* Ar-H), 8.90 (s, 1H, pyrazolyl), 10.41 (s, 1H, NH)**.**

**13C NMR (DMSO-d6) δ** = 65.85 (N-CH2), 79.19 (O-CH2), 113.51 (C4-pyrazolyl), 123.45 (CH=), 129.69 (C5-pyrazolyl), 132.42 (CH=C), 149.26 (C3-pyrazolyl), (114.33, 118.65, 124.32, 126.75, 128.05, 128.43, 128.74, 129.04, 129.46, 138.72, 139.24, 151.60) Ar-C, 164.10 (CO-NH), 166.77 (CO-moropholine).

**MS: *m/z* (%) =** 524 (M++1, 1.03), 523 (M+, 3.03), 437 (30,26), 436 (100), 408 (8.47), 258 (46.37), 150 (17.35), 104 (19.85), 77 (18.54), 76 (11.11).

**Anal. Calcd for C29H25N5O5 (523.55) =** C, 66.53; H, 4.81; N, 13.38 %.

**Found =** C, 66.50; H, 4.66; N, 13.40 %.

**Synthesis of** (***E*)-*N*-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-oxo-3-(piperidin-1-yl)prop-1-en-2-yl)-4-nitrobenzamide (9d)**

Pale yellow, mp 264 - 266°C.

Yield =64%.

**IR** (νmax, cm-1): 3124 (NH), 2940, 2850 (CH-aliphatic), 1678, 1600 (2CO amides), 1546 (C=C), 754,695 (monosubstituted benzene), 850 (*p*-disubstituted benzene)**.**

**1HNMR (DMSO-d6)**: δH (ppm): 1.54 (br.m, 2H, N-CH2-CH2-CH2), 3.33 – 3.64 (br.m, 8H, -N-CH2CH2), 6.20 (s, 1H, CH=), 7.36 (t, 1H, *J=7.5 Hz,* Ar-H), 7.41 (t, 1H, *J=7.5 Hz,* Ar-H), 7.46 – 7.53 (m, 4H, Ar-H), 7.64 (d, 2H, *J=8 Hz,* Ar-H), 7.87 (d, 2H, *J=7.5 Hz,* Ar-H), 8.14 (d, 2H, *J = 9 Hz,* Ar-H), 8.32 (d, 2H, *J=9 Hz,* Ar-H), 8.89 (s, 1H, pyrazolyl), 10.36 (s,1H, NH).

**13CNMR (DMSO-d6) δ =** 24.19 (C4- piperidine), 25.25 (C3,5- piperidine), 41.55 (C2,6- piperidine), 112.88 (C4-pyrazolyl), 123.44 (CH=), 129.69 (C5-pyrazolyl), 132.43 (CH=C), 149.21(C3-pyrazolyl), (114.42, 118.64, 126.72, 127.41, 128.04, 128.41, 128.62, 128.73, 129.42, 138.91, 139.26, 151.57) (Ar-C), 163.90 (CO-NH), 166.42 (CO-N).

**MS: *m/z* (%) =** 522 (M++1, 0.23), 521 (M+, 0.60), 437 (29.73), 436 (100), 259 (19.39), 258 (89.81), 150 (30.29), 105 (3.06), 104 (37.83), 92 (12.70), 78 (3.44), 77 (44.81), 76 (21.68), 69 (4.46).

**Anal. Calcd for C30H27N5O4 (521.58) =** C, 69.08; H, 5.22; N, 13.43 %.

**Found** = C, 69.20; H, 5.11; N, 13.25 %.

**Synthesis of (*E*)-*N*-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-oxo-3- (phenyl amino) prop-1-en-2-yl)-4-nitrobenzamide (10)**

A mixture of oxazolone **3** (4.36 g, 0.01 mol) and aniline (1.40 g, 0.015 mol) in EtOH: DMF (1:2) was refluxed for 10 h and left overnight, then reaction mixture was poured into water and to give yellow precipitate which recrystallized from EtOH to yield compound **10**.

Bright yellow, mp 265 - 266°C.

Yield =50%.

**IR** (νmax, cm-1): 3268 (NH), 1658,1626 (2CO amides), 1598 (C=C), 746, 702 (monosubstituted benzene), 846 (*p*-disubstituted benzene).

**1HNMR (DMSO-d6)**: δH (ppm): 7.06 (t, 1H, *J = 7 Hz*, Ar-H), 7.11 (s, 1H, CH=), 7.29 – 7.36 (m, 3H, Ar-H), 7.43 (t, 1H, *J = 8 Hz*, Ar-H), 7.50 (t, 4H, *J = 7.5 Hz*, Ar-H), 7.68 (m, 4H, *J = 8 Hz*, Ar-H), 7.81 (d, 2H, *J = 7.5 Hz*, Ar-H), 8.25 (d, 2H, *J = 8 Hz*, Ar-H), 8.37 (d, 2H, *J = 8.5 Hz*, Ar-H), 8.77 (s, 1H, pyrazolyl), 10.11 (s, 1H, Ph-NH), 10.30 (s, 1H, NH-CO)**.**

**13CNMR (DMSO-d6)** δ = 114.75 (C4-pyrazolyl), 123.42 (CH=), 130.10 (C5-pyrazolyl), 132.26 (CH=C), 149.23 (C3-pyrazolyl), (118.75, 119.12, 120.19, 123.42, 126.98, 127.32, 128.28, 128.56, 128.65, 128.84, 129.52, 129.74, 139.10, 139.17, 139.34, 152.36) Ar-C, 163.54 (Ph-CO-NH-), 164.27 (Ph-NH-CO).

**MS: *m/z* (%) =** 530 (M++1, 1.86), 529 (M+, 5.26), 511(4.70), 438 (5.42), 437 (26.69), 436 (54.50), 286 (4.93), 260 (6.65), 259 (27.72), 258 (97.95), 155 (18.52), 151 (8.65), 150 (95.73), 128 (10.04), 120 (36.65), 104 (91.05), 105 (8.03), 103 ( 9.05), 93 (84.72), 92 (42.26), 77 ( 100.0), 78 (9.15), 66 (18.27), 65 (15.58).

**Anal. Calcd for C31H23N5O4 (529.56) =** C, 70.31; H, 4.38; N, 13.23 %.

**Found** = C, 70.42; H, 4.41; N, 13.45 %.

**Synthesis of (*E*)-4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-6-(4-nitrophenyl)-2*H*-1,2,5-oxadiazin-3(4*H*)-one (11)**

A mixture of oxazolone **3** (4.36 g,0.01 mol) in pyridine (30 mL) and hydroxylamine hydrochloride (1.04 g, 0.015 mol) was heated under reflux for 8h. The reaction mixture was left to cool, then it was poured into crushed ice and neutralized with conc. HCl. The precipitate was filtered off, washed with water and recrystallized from MeOH to produce **11**.

Orange powder, mp 368 - 370°C.

Yield = 70%.

**IR** (νmax, cm-1): 3202 (NH), 1691 (CO), 1630 (C=C), 773,694 (monosubstituted benzene), 850 (*p*- disubstituted benzene).

**1HNMR (DMSO-d6)**: δH (ppm): 7.18 (s, 1H, CH=), 7.45 (t, 1H, *J = 7.5 Hz*, Ar-H), 7.58 – 7.61 (m, 5H, Ar-H), 7.70 (d, 2H, Ar-H), 8.01 (d, 2H, *J = 7.5 Hz*, Ar-H), 8.43 (dd, 2H, *J = 8.5 Hz*, Ar-H), 8.60 (dd, 2H, *J = 9 Hz*, Ar-H), 9.36 (s, 1H, pyrazolyl), 11.55 (s, 1H, NH).

**13CNMR (DMSO-d6)** δ **=** 115.44 (CH=), 119.59 (C4-pyrazolyl), 130.13 (C5-pyrazolyl), 138.81 (C4-triazine), (120.89, 123.87, 127.70, 128.78, 129.06, 129.12, 129.80, 131.42, 131.86, 132.97, 134.05, 149.16) (Ar-C), 154.54 (C3-pyrazolyl), 155.05 (C2-triazine), 165.16 (CO).

**MS: *m/z* (%) =** 452 (M++1, 4.94), 451 (M+, 15.70), 436 (30.02), 435 (65.93), 406 (12.37), 259 (23.96), 258 (29.85), 231(13.72), 155 (15.26), 150 (12.46), 104 (31.39), 103 (29.44), 93 (15.95), 77 (100), 76 (34.00).

**Anal. Calcd for C25H17N5O4 (451.44) =** C, 66.51; H, 3.80; N, 15.51 %.

**Found** = C, 66.61; H, 3.91; N, 15.66 %.

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