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Synthesis and reactions of oxadiazolo, thiadiazolo and triazolo phthalazin-1(2*H*)-one derivatives

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ABSTRACT

*Reaction 2-{2,3-dichlorophenylcarbonyl}-benzoic acid **1** with hydroxylamine hydrochloride in boiling pyridine afforded 4-(2,3dichlorophenyl)-1H-2,3-benzoxazin-1-one **2** which on condensation with ethyl glycinate in the presence of sodium acetate gave ethyl[4-(2,3-dichlorophenyl)-1-oxophthalazin-2(1H)-yl)]acetate **3**. The sulphonamide derivative **5** was prepared via the reaction of acid hydrazide **4** with p- toluene sulfonyl chloride in refluxing glacial acetic acid. Also, oxadiazole **6** was preformed through the reaction of the acid hydrazide **4** with ethyl chloroformate under reflux in n-butanol. N-amino 4-(2, 3-dichlorophenyl)-2-[5-oxo-4, 5-dihydro1, 3, 4-triazol-2-yl) methyl] phthalazin-1-(2H)-one **7** was prepared via condensation of oxadiazole **6** with hydrazine hydrate in boiling n-butanol. Thiadiazole drevative **10** was prepared by stirring the dithiacarbazate **8** with conc. H_2SO_4 at room temperature while on refluxing **8** in absolute ethanol afforded the oxadiazole **11**. Each of **8**, **10** and **11** on hydrazinolysis with hydrazine hydrate gave 2-(4-amino 5-thioxo-4, 5-dihydro-1H-1, 2, 4-triazol-3-yl) 4-(2, 3 dichlorophenyl)-phthalazin-1-(2H)-one **12**. Thiourea derivative **15** was prepared by the reaction of **12** phenyl isothiocyanate in refluxing DMF. The structure of all compounds was confirmed from their correct analytical and spectral data.*

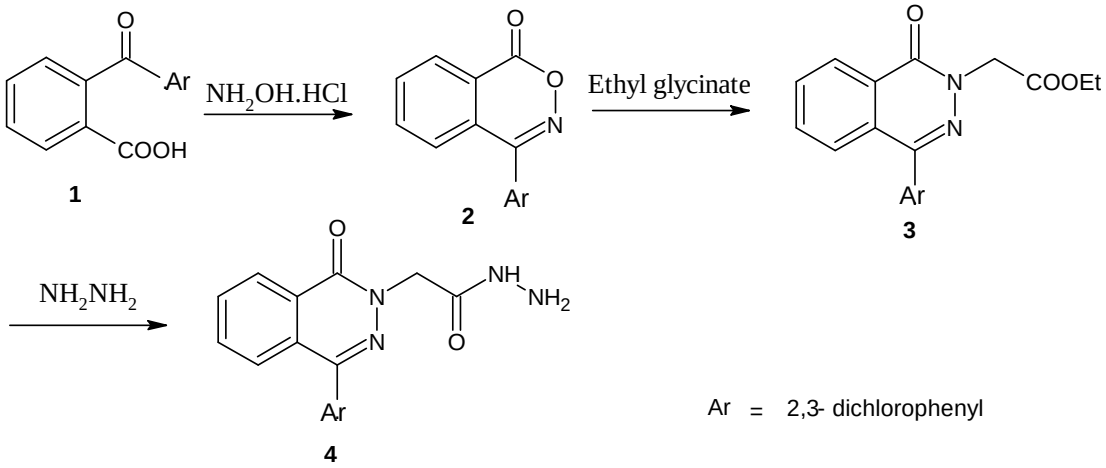
Keywords: Phthalazinone, thiazoles, ethyl glycinate, oxadiazoles, thiadiazole, triazole, anti-inflammatory, antihypertensive activity.

INTRODUCTION

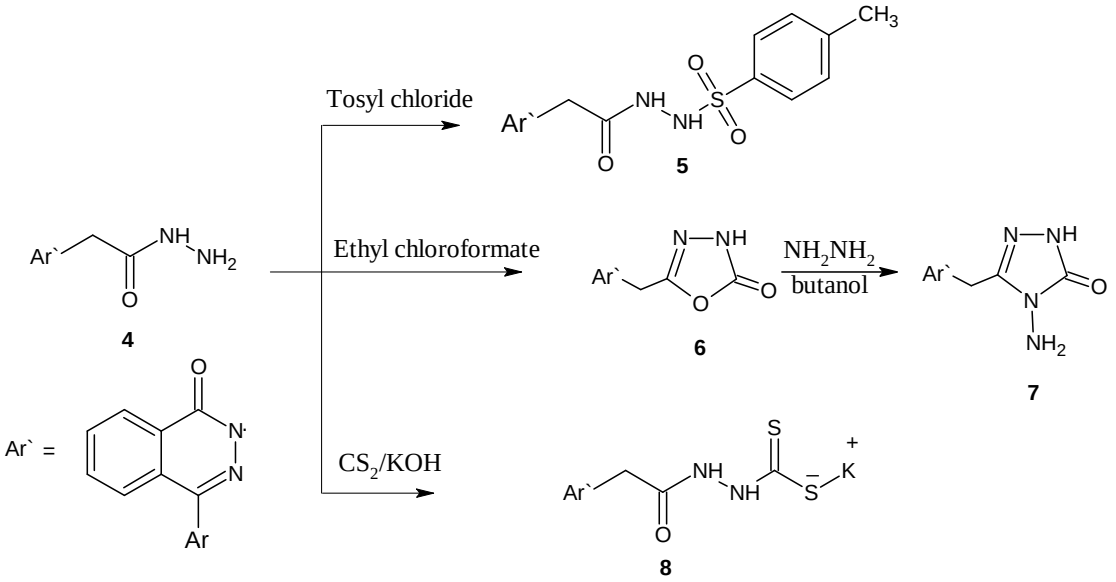
It is well known that phthalazinone derivatives have considerable biological and pharmaceutical activities, such as antimicrobial, vasodialator , anti- hypertensive properties [1-2] (T. L. Gilchrist et al. 1997) and as the blood platelet aggregation inhibitor [3] (M. Napoletano et al.,2001).. In continuation to our previous studies [4-6] (F. A. Yassin, at al.,1992) the present research work was focus mainly on synthesis of a new series of phthalazin -1(2H)-ones. Hence, research was designed to synthesis phthalazinones attached to heterocyclic moieties in position -2 such as oxadiazoles, thiadiazoles and triazoles due to their anti-inflammatory activities. Both phthalazinones and the heterocyclic moieties feeding off of the synergistic effect of the other.

In the present research work, the starting material 2-(2,3-dichlorophenylcarbonyl)-benzoic acid **1** was prepared through the reaction of phthalic anhydride with o-dichlorobenzene in the presence of $AlCl_3$ under Friedel-Craft's reaction conditions. The reaction 2-(2,3dichlorophenylcarbonyl) -benzoic acid **1** with hydroxylamine hydrochloride in boiling pyridine[7] (Zentymyer et al., 1949). afforded 4-(2,3-dichlorophenyl) -1*H*-2,3-benzoxazin-1-one **2** which on condensation with ethyl glycinate in the presence of sodium acetate[8](J. Ponda et al. , 2002) gave ethyl-[4-(2,3-dichlorophenyl)-1-oxophthalazin-2(1*H*)-yl)]acetate **3**. The structure of **3** was confirmed from its correct analytical and spectral data. IR spectrum of **3** showed absorption bands at 1725(C=O ester), 1665(C=O) and1645 (C=N). ^{1}HNMR spectrum of **3** showed signals at δ =1.3(t, 3H, CH2-$\underline{CH_3}$) 4.3(q, 2H, $\underline{CH_2}$-CH_3), 5.1(s, 2H, CH_2-), and 7.3-7.8 (m, 7H aromatic protons).

Ethyl [4-(2, 3-dichlorophenyl)-1-oxophthalazin-2(1*H*)-yl)] acetate **3** on reaction with hydrazine hydrate in boiling ethanol afforded the corresponding 2-[4-(2,3 -dichlorophenyl)-1-oxophthalazin-2(1*H*)-yl)]acetohydrazide **4**. The structure of **4** was confirmed from its correct analytical and spectral data. IR spectrum of **4** showed absorption bands at 3300, 3308(NH_2), 3165(NH) 1675, 1660(2C=O) and1645 (C=N). ^{1}HNMR spectrum of **4** showed signals at 4.1(s, 2H, CH_2-), 4.7(s, 2H, NH_2), 7.4-8.0 (m, 7H aromatic protons) and 9.4 (s, 1, NH).



Scheme 1



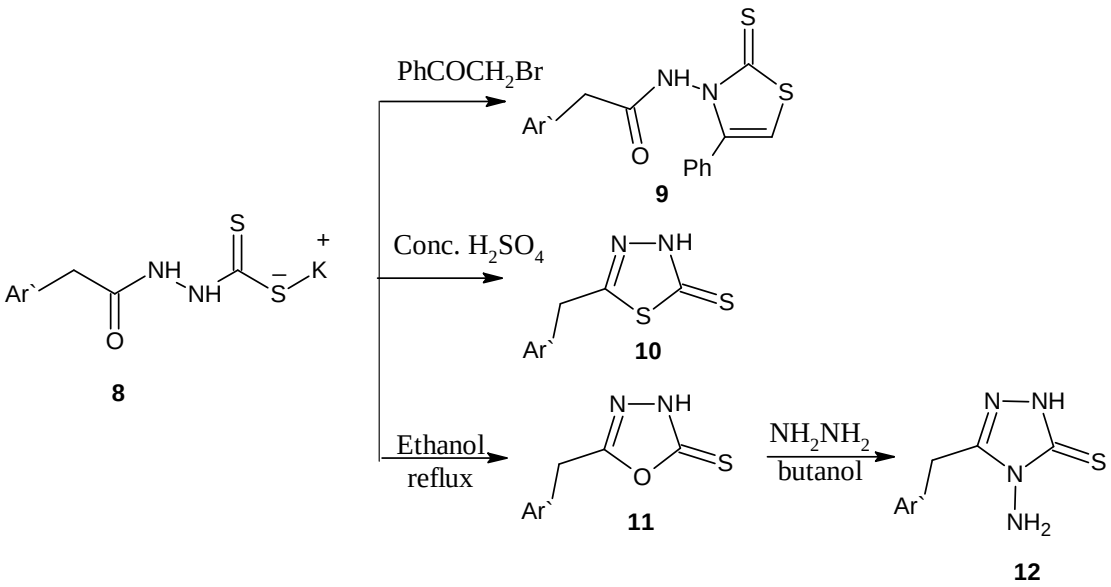
Scheme 2

Sulfone derivatives are well known by their interesting antibacterial and antifungal activities. Efforts have been and still being made to enhance their antibacterial and antifungal activities for medical and hygienic applications[9] (T. Osten, et al., 2004).

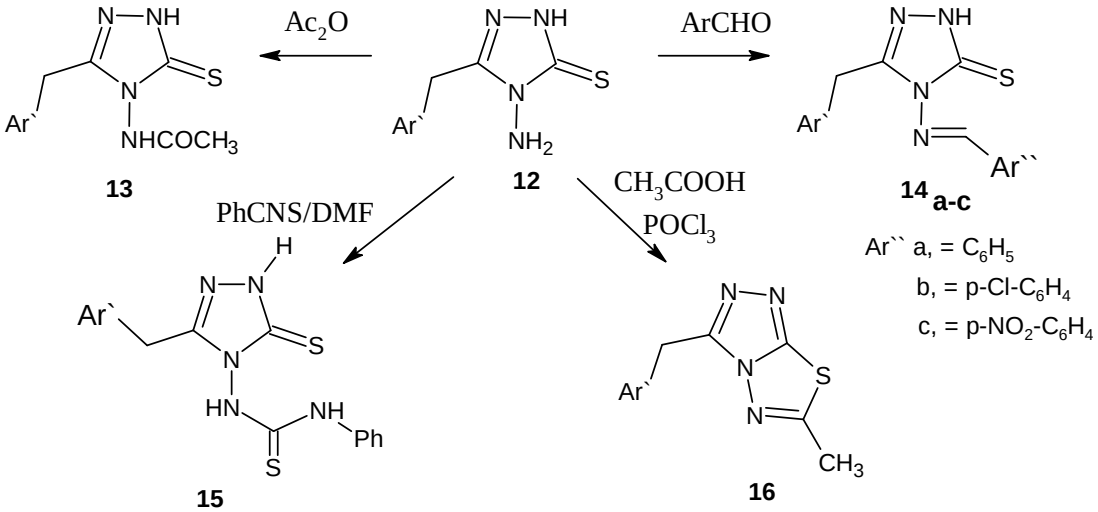
With this in mind, this research work was design to prepare N'-(2-[4-(2, 3- dichlorophenyl)-1-oxophthalazin-2(1*H*)-yl)]acetyl4-methylbenzenesulfonyl hydrazide **5** via the reaction of acid hydrazide **4** with p- toluene sulfonyl chloride in refluxing glacial acetic acid[10] (M. K. Parai, et al.,2008). The structure of **5** was confirmed from its correct analytical and spectral data. IR spectrum of **5** showed absorption bands at 3300, 3170(2NH), 1701, 1675, 1660(2C=O) and1645 (C=N), 1339, 1160(SO_2). ^{1}HNMR spectrum of **5** showed signals at δ =2.3(s, 3H, CH_3), 4.7(s, 2H, CH_2-), 7.3-8.2 (m, 11H aromatic protons) and 9.6, 10.5(s, 2H, 2NH).

It has been reported that, 1,3,4- oxadiazoles exhibit a wide therapeutic activities as anti-inflammatoryactivity [11] (S. V. Bhndari , et al., 2008). Hence, in this investigation the 4-(2, 3-dichlorophenyl)-2-[5-oxo-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl) methyl] phthalazin-1-(2*H*)-one **6** was synthesized through the reaction of the acid hydrazide **4** with ethyl chloroformate under reflux in n-butanol. IR spectrum of **6** showed absorption bands at 3170(NH) , 1708,

1690(2C=O) and1645 (C=N). ^{1}HNMR spectrum of **6** showed signals at δ = 5.1(s, 2H, CH_2-), 7.3-7.9 (m, 7H aromatic protons) and 10.6 (s,1H, NH).



Scheme 3



Scheme 4

Heterocycles bearing triazole moieties represent an interesting class of compounds possessing a significant anti-inflammatory activity [12] (B. Berk, et al.,2001). Therefore, in this work, 2-(4-amino 5-oxo-4, 5-dihydro-1*H*-1, 2, 4-triazol-3-yl) 4-(2, 3dichlorophenyl)-phthalazin-1-(2*H*)-one **7** was prepared via condensation of oxadiazole **6** with hydrazine hydrate in boiling n- butanol. The structure of **7** was confirmed from its correct analytical and spectral data. IR spectrum of **7** showed absorption bands at 3300(NH2), 3290, 3198(NH), 1675, 1660(2C=O) and 1645 (C=N). ^{1}HNMR spectrum of **7** showed signals at δ = 5.1(s, 2H, CH_2-), 5.8(s, 2H, NH_2), 7.3-7.8 (m, 10H aromatic protons) and 10.8 (s, 1H, NH). **(Scheme 2)**

On the other hand, 1,3-thiazoles were reported to exhibit an excellent anti-inflammatory activity[13] (H.M.Vagdevi, et al.,2006). Thus, it was interesting to synthesize novel 1,3-thiazoles product through the reaction of the acid hydrazide **4** with CS_2 in the presence of KOH to give potassium 2{-[4-(2,3-dichlorophenyl)-1-oxophthalazin-2-(1*H*)-yl)]acetyl} hydrazino- cabodithioate **8** which on cyclization with phenacyl bromide [14] (A. R. Katritzky.et al., 2003) in refluxing pyridine afforded N- [4-(2, 3dichlorophenyl)(2-thioxo-2,3-dihydro-2-phenyl 1, 3, -thiazol-1-yl)acetamido] phthalazin-1-(2*H*)-one **9**. The structure of **9** was confirmed from its correct analytical and spectral data. IR spectrum of **9** showed absorption bands at 3170(NH), 1675(C=O) and1645 (C=N) and1350(C=S). ^{1}HNMR spectrum of **9** showed signals at δ =5.1(s, 2H, CH_2-), 6.1(s, 1H, CH), 7.1-7.8 (m, 12H aromatic protons) and 10.8(s,1H,NH).

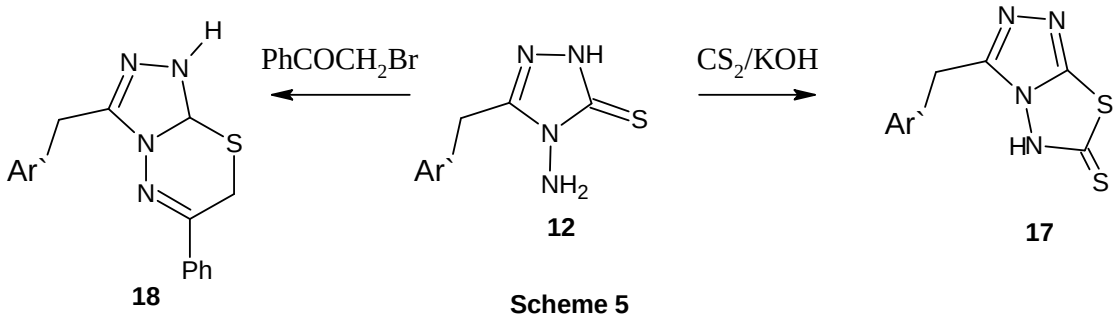
Due to the remarkable anti-inflammatory activity of the thiadiazole, and to increase this properties for medical and hygienic applications, we planned to synthesis thiadiazole compounds. The experimental technique was adopted as follows: 4- (2, 3 -Dichlorophenyl)-2-[5-thioxo 4, 5-dihydro1,3,4-thiadiazol-2-yl)methyl]phthalazin-1-(2*H*)-one **10** was prepared by stirring the dithiacarbazate **8** with conc. H_2SO_4 at room temperature[15](R. W. Young , et al.,1955). IR spectrum of **10** showed absorption bands at 3170(NH), 1680(C=O) and1645 (C=N) and1350(C=S). ^{1}HNMR spectrum of **10** showed signals at δ =4.9(s, 2H, CH_2-), 7.2-7.8 (m, 7H aromatic protons) and 10.6(s, 1H,NH),while on refluxing **8** in absolute ethanol[19] afforded 4-(2,3-dichlorophenyl)-2-[5-oxo4,5dihydro1,3,4oxadiazol-2-yl)methyl]phthalazin-1-(2*H*)-one **11**. Each of **8**, **10** and **11** on hydrazinolysis with hydrazine hydrate in refluxing n-butanol gave 2-(4-amino 5-thioxo-4, 5-dihydro-1*H*-1, 2, 4-triazol-3-yl) 4-(2, 3dichlorophenyl)-phthalazin-1-(2*H*)-one **12**. IR spectrum of **12** showed absorption bands at 3310-3284(NH_2), 1690 (C=O) and1645 (C=N) . ^{1}HNMR spectrum of **12** showed signals at δ =5.3(s, 2H,CH_2-) , 6.1(s, 1H, NH_2), 7.4-8.1 (m, 7H aromatic protons) and 12.6(s,1H,NH). **(Scheme3)**

Chemical the structure of **12** was confirmed through its reaction with acetyl chloride to give N-acetyl derivative **13**. Also, condensation of aminotriazole **12** with the appropriate aldehyde namely benzaldehyde , p-chloro and p-nitro-benzaldehyde in refluxing ethanol and few drops of acetic acid gave the corresponding 4-(2, 3dichlorophenyl)-2{E-(substitutedphenyl) methylidene} amino-[(5-oxo-4, 5-dihydro1, 3, 4oxadiazol-2-yl)methyl] phthalazin-1-(2H)-one **14a-c** .IR spectrum of **14a** showed bands at, 3215(NH),2550(SH) 1690(C=O) and1605 cm^{-1} (C=N). While ^{1}H-NMR spectrum of **14c** showed signals at δ = 5.2(s, 2H, CH_2-), 7.5-8.1 (m, 11H aromatic protons), 9.5(s, 1H, CH=N), 11.2(s, 1H,NH).

Thiourea derivatives are of much importance being used as neutral acceptors for various anions and as synthetic intermediate, herein the thiourea derivative **15** was prepared by the reaction of 2-(4-amino 5-thioxo-4, 5-dihydro-1*H*-1, 2, 4-triazol-3-yl) 4-(2, 3-dichlorophenyl)-phthalazin-1-(2*H*)-one **12** with phenyl isothiocyanate [16] (M. Palko, et al., 2005**)** in refluxing DMF . The structure of **15** was confirmed from its correct analytical and spectral data. IR spectrum of **15** showed absorption bands at 3222, 3170, 3122(3NH), 1675(C=O) and1645 (C=N) and1324(C=S). ^{1}HNMR spectrum of **15** showed signals at δ =5.3(s, 2H, CH_2-), 7.3-7.8 (m, 12H aromatic protons) and 10.1(s, 1H,NH), 11.5-12.1(b,2H,2NH). **(Scheme 4)**

Cyclization of **12** in the presence of acetic acid and $POCl_3$ gave the corresponding 4-(2,3-dichlorophenyl)-2-[6-methyl-1,2,4triazol[3,4-*b*][1,3,4-thiadizol-3-yl)methyl)- phthalazin-1-(2*H*)-one **16**. IR and ^{1}HNMR spectra of **16** confirmed the success of the cyclization of the aminotriazole **12** indicating the disappearance of the signals of NH and $NH_2$and appearance of a signal at 2.8 assigned to methyl protons.

It was reported that, 4-amino-1,2,4-triazole-3- thione derivatives on condensation with carbon disulphide in basic media produce the corresponding triazolothiadiazoles. therefore, on reaction of the 2-(4-amino 5-thioxo-4, 5-dihydro-1*H*-1, 2, 4-triazol-3-yl) 4-(2, 3-dichlorophenyl)-phthalazin-1-(2*H*)-one **12** with C_2S in refluxing ethanol[17] (Z. K. Abd El-Samie, et al., 1987) containing KOH gave 4-(2,3-dichlorophenyl)-2-[6-thioxo-5,6-dihydro-1,2,4triazol[3,4-b][1,3,4-thiadizol-3-yl)methyl)- phthalazin-1-(2*H*)-one **17 .** IR and ^{1}HNMR spectra confirmed the structure of **17** through the disappearance of the signals NH_2 group.



18 **12** **17**

Scheme 5

Recently, it was reported that the reaction of 4-amino-1,2,4-triazole-3- thione derivatives with phenacyl bromide furnishes 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines, thus in the present investigation the reaction of the 2-(4-amino 5-thioxo-4, 5-dihydro-1*H*-1, 2, 4-triazol-3-yl) 4-(2, 3-dichlorophenyl)-phthalazin-1-(2*H*)-one **12** undergo cyclocondensation with phenacyl bromide in refluxing ethanol afforded 4-(2,3dichlorophenyl)-2-[6-phenyl-1,2,4-triazol[3,4-b][1,3,4-thiadiazin-3-yl]methyl)- phthalazin-1-(2*H*)-one **18**. IR and ^{1}HNMR spectra of **18** confirmed the success of the cyclization of the aminotriazole **12** indicating the disappearance of the signals NH_2 group, and appearance of a signal at 3.8 assigned to S-CH_2- protons. **(Scheme 5)**

MATERIALS AND METHODS

All melting points were uncorrected. IR spectra were measured using KBr disc plate technique on a Bruker FT-IR ISS 25 spectrophotometer (ν_{max} in cm^{-1}). ^{1}HNMR spectra (DMSO-d_6 and $CDCl_3$) were carried out on a Bruker Avance 200 MHz spectrometer using TMS as internal reference (chemical shifts in δ, ppm).

4-(2, 3Dichlorophenyl)-1*H*-2, 3-benzoxazin-1-one 2:
A mixture of o-aroyl benzoic acid **1** (0.02 mole) in dry pyridine (20 ml) and hydroxylamine hydrochloride (0.02 mole) was refluxed for 3 hours. The reaction mixture was cooled, then poured over ice-cold dil. HCl. The solid separated was filtered washed with water, dried and crystallized from ethanol.
M.P. = 181^{0}C, yield 70 %. Analysis: $C_{14}H_7Cl_2NO_2$ (292.11).
Calcd.: C = 57.56 H= 2.42 N= 4.79 Found: C = 57.20 H= 2.39 N= 4.74

Ethyl [4-(2,3dichlorophenyl)-1-oxophthalazin-2(1*H*)-yl)]acetate 3:
To a solution of **1** (0.02 mole) in absolute ethanol (20 ml) a mixture of ethyl glycinate and sodium acetate (0.02 mole) was added. The reaction mixture was refluxed for 2 hours. The reaction mixture was cooled to room temperature then poured in ice cold water. The resulting solid was filtered washed with water, dried and crystallized from ethanol.
M.P. = 145^{0}C, yield 75 % Analysis: $C_{18}H_{14}Cl_2N_2O_3$ (377.22).
Calcd.: C = 57.31 H= 3.74 N= 7.43 Found: C = 57.28 H= 3.71 N= 7.40

2-[4-(2,3-Dichlorophenyl)-1-oxophthalazin-2(1*H*)- yl)]acetohydrazide 4:
To a solution of the ester **3** (0.02 mole) in absolute ethanol (20 ml) hydrazine hydrate (0.02 mole) was added. The reaction mixture was refluxed for 5hours. The solid separated was filtered washed with water, dried and crystallized from ethanol.
M.P. = 260^{0}C, yield 70 %. Analysis: $C_{16}H_{12}Cl_2N_4O_2$ (363.19).
Calcd.: C = 52.91 H= 3.33 N= 15.43 Found: C = 52.87 H= 3.30 N= 15.39

N'-(2-[4-(2, 3 -Dichlorophenyl)-1-oxophthalazin-2(1*H*)-yl)]acetyl 4-methyl benzenesulfonyl hydrazide 5:
To a solution of the acid hydrazide **4** (0.02 mole) in glacial acetic acid (30 ml), p-toluene sulfonyl chloride (0.02 mole) was added. The reaction mixture was stirred at room temperature overnight, water was added and the precipitate obtained was filtered off dried and crystallizes from ethanol.
M.P. = 245^{0}C, yield 76 %. Analysis: $C_{23}H_{18}Cl_2N_4O_4S$ (517.38).
Calcd.: C = 53.39 H= 3.51 N= 10.83 S= 6.20 Found: C = 53.31 H= 3.50 N= 10.80 S= 6.15

4-(2, 3-Dichlorophenyl)-2-[5-oxo4, 5-dihydro1, 3, 4-oxadiazol-2-yl)methyl] phthalazin-1-(2*H*)-one 6:
A mixture the acid hydrazide **4** (0.02 mole) and ethyl chloroformate (0.02 mole) in n- butanol (20ml) was refluxed with stirring for 20 hours ,then the reaction mixture was cooled. The resulting solid was filtered washed with ethanol, dried and crystallized from acetic acid.
M.P. > 300^{0}C, yield 58 %. Analysis: $C_{17}H_{10}Cl_2N_2O_3$ (389.19).
Calcd.: C = 52.46 H= 2.59 N= 14.40 Found: C = 52.42 H= 2.56 N= 14.40

2-(4-Amino 5-oxo-4, 5-dihydro-1*H*-1, 2, 4-triazol-3-yl) 4-(2, 3-dichlorophenyl)-phthalazin-1-(2*H*)-one 7:
A mixture oxadizole **6** (0.02 mole) and hydrazine hydrate (0.02 mole) in n- butanol (20ml) was refluxed with stirring for 15 hours ,then the reaction mixture was cooled. The resulting solid was filtered washed with ethanol, dried and crystallized from ethanol.
M.P. 155^{0}C, yield 66 %. Analysis: $C_{17}H_{12}Cl_2N_6O_2$ (403.22).
Calcd.: C = 50.64 H= 3.00 N= 20.84 Found: C = 50.60 H= 3.00 N= 20.81

Potassium 2-{-[4-(2,3-dichlorophenyl)-1-oxophthalazin-2- (1*H*)-yl)]acetyl} hydrazinecabodithioate 8:
Carbon disulfide (0.02 mole) was added drop wise to an ice cooled solution of KOH (2g) in ethanol (20 ml) containing the acid hydrazide **4** (0.02 mole), then the reaction mixture was stirred at room temperature 12 hours . After dilution with ethanol the solid precipitated was washed twice with ether. The resulting solid was used in the next reaction .

N- [4-(2, 3-Dichlorophenyl)(2-thioxo-2,3-dihydro-2-phenyl 1, 3, -thiazol-1-yl) acetamido] phthalazin-1-(2*H*)-one 9:
To a cold solution of the dithiacarbazate **8** (1g) in 1,4-dioxane (20 ml), phenacyl bromide (0.02 mole) was added. The reaction mixture stirred at room temperature over night, then after acidification with conc.HCl the solid separated was washed with water, filtered, dried and crystallized from ethanol.

M.P. 216°C, yield 76 %. Analysis: $C_{25}H_{16}Cl_2N_4O_2S_2$ (539.45).
Calcd.: C = 55.66 H= 2.99 N= 10.39 Found: C = 55.63 H= 2.99 N= 10.35

4- (2, 3- Dichlorophenyl)-2-[5-thioxo 4, 5-dihydro1,3,4-thiadiazol-2-yl)methyl] phthalazin-1-(2*H*)-one 10:
A cold solution of the dithiacarbazate **8** (1g) in absolute ethanol (20 ml), was refluxed for 10 hours till the evolution of hydrogen sulphide ceased. The reaction mixture was concentrated, dissolved in water, then after acidification with conc.HCl the solid separated was washed with water, filtered, dried and crystallized from ethanol.
M.P. 250°C, yield 60 %. Analysis: $C_{17}H_{10}Cl_2N_4OS_2$ (421.32).
Calcd.: C = 48.46 H= 2.39 N= 13.30 S= 15.22 Found: C = 48.44 H= 2.37 N= 13.25 S= 15.20

4-(2, 3-Dichlorophenyl)-2-[5-oxo4,5dihydro1,3,4oxadiazol-2-yl)methyl] phthalazin-1-(2*H*)-one 11:
A cold solution of the dithiacarbazate **8** (1g) was added dropwise to ice cold concentrated H_2SO_4 (10ml) with continuous stirring over night, then gradually added to cruched ice .The solid separated was washed with water , filtered off, dried and crystallized from ethanol.
M.P. 265°C, yield 50 %. Analysis: $C_{17}H_{10}Cl_2N_4O_2S$ (405.25).
Calcd.: C = 50.38 H= 2.49 N= 13.82 S= 7.9 Found: C = 50.34 H= 2.46 N= 13.80 S= 7.89

N- Amino-4-(2, 3-dichlorophenyl)-2-[(5-thioxo-4, 5dihydro1, 3, 4oxadiazol-2-yl)methyl] phthalazin-1-(2*H*)-one 12:
A mixture of the dithiacarbazate **8** (1g) in absolute ethanol (20 ml), and hydrazine hydrate (0.02 mole) was refluxed for 10 hours. The reaction mixture was cooled to room temperature, dissolved in water, then after acidification with concentrated HCl the solid was separated, washed with water, filtered off, dried and finally crystallized from ethanol.
M.P. 155°C, yield 72 %. Analysis: $C_{17}H_{12}Cl_2N_6OS$ (419.28).
Calcd.: C = 47.70 H= 2.88 N= 20.04 S= 7.65 Found: C = 47.67 H= 2.85 N= 20.00 S= 7.60

N-(3-{[4-(2,3-Dichlorophenyl)-2-[5-oxo phthalazin-1-(2H)-one-2-yl] methyl} -4,5dihydro-4*H*-1,2,4triazol-4-yl)acetamide 13:
Compound **12** (0.02 mole) was refluxed in acetic anhydride (20ml) for 5 hours. After cooling, the reaction mixture was neutralized with ammonium hydroxide; the precipitate was collected by filtration, washed with water and crystallized from ethanol.
M.P. 282°C, yield 66 % . Analysis: $C_{15}H_{14}Cl_2N_6O_2S$ (461.32).
Calcd.: C = 49.47 H= 3.06 N= 18.22 S= 6.95 Found: C = 49.43 H= 3.04 N= 18.18 S= 6.90

4-(2, 3-Dichlorophenyl)-2{E-(substitutedphenyl)methylidene}amino-[(5-oxo-4, 5-dihydro1, 3, 4oxadiazol-2-yl)methyl] phthalazin-1-(2H)-one 14a-c:
To a solution of the aminotriazole **12** (0.01 mol) in 30 ml ethanol and few drops of acetic acid, (0.02 mole) of aromatic aldehydes namely benzaldehyde, p-chlorobenzaldehyde and p-nitrobenzaldehyde was added. The reaction mixture was heated under reflux for 5 hrs, and then cooled. The separated solids were filtered, dried and crystallized from acetic acid.
M.P. **14a**: 275°C, **14b**: 235°C **14c**: 281°C, yield 71 %, 60 and 65 respectively.
Analysis: **14a**: $C_{24}H_{16}Cl_2N_6OS$ (507.39), **14b**: $C_{24}H_{15}Cl_3N_6OS$ (541.83)**14c**: $C_{24}H_{15}Cl_2N_7O3S$ (552.39)
Calcd.: **14a** C = 56.81 H = 3.18 N = 16.56 S=6.32 Found: C = 56.79 H = 3.10 N = 16.50 S= 6.29
14b Calcd., C = 53.20 H = 2.79 N = 15.51 S= 5.92 Found : C = 53.10 H = 2.74 N = 15.48 S= 5.87
Calcd.: **14c** C = 52.18 H = 2.74 N = 17.75 S=5.80 Found : 52.09 H = 2.70 N = 17.65 S= 5.70

1-(3-{[4-(2, 3Dichlorophenyl)-1-oxo phthalazin-1-(2H)-one-2-yl] methyl} -5-thioxo-1H-1, 2, 4-triazol-4(5H)-yl)-3-phenylthiourea 15:
To a solution of the aminotriazole **12** (0.02 mole) in DMF (30 ml), phenyl isothiocyanate (0.02 mole) was added. The reaction mixture was stirred at room temperature overnight, water was added and the precipitate obtained was filtered off dried and crystallizes from ethanol.
M.P: 185°C, yield 81 %. Analysis: $C_{24}H_{17}Cl_2N_7OS_2$ (554.47).
Calcd.: C= 51.99 H = 3.09 N = 17.68 S=11.57 Found: C= 51.91 H = 3.00 N = 17.61 S=11.50

4-(2,3-Dichlorophenyl)-2-[6-methyl-1,2,4triazol[3,4-b][1,3,4-triazolo-3-yl) phthalazin-1-(2*H*)-one 16:
To a solution of the aminotriazole **12** (0.02 mole) in acetic acid (20 ml), phosphorus oxychloride (0.02 mole) was added. The reaction mixture was rfluxed for 5 hours on a water bath, then the reaction mixture was slowly poured into crushed ice with stirring and neutralized with sodium bicarbonate. The precipitate obtained was filtered off, washed with water, dried and crystallizes from ethanol
M.P. 190°C, yield 56 %. Analysis: $C_{19}H_{12}Cl_2N_6OS$ (443.30).

Calcd.: C=51.48 H = 2.73 N = 18.96 S=7.23 Found: C=51.44 H = 2.70 N = 18.91 S=7.20

4-(2,3-Dichlorophenyl)-2-[6-methyl-1,2,4triazol[3,4-b][1,3,4-triazolo-3-yl) phthalazin-1-(2*H*)-one 17:
The aminotriazole **12** (0.02 mole) was dissolved in absolute ethanol (20 ml) containing 1g of KOH, carbon disulfide (2 ml) was added then the reaction mixture was refluxed for 6 hours . The reaction mixture was concentrated, dissolved in water, then after acidification with concentrated HCl the solid separated was washed with water, filtered, dried and crystallized from ethanol.
M.P. 250^{o}C, yield 60 %. Analysis: $C_{18}H_{10}Cl_2N_6OS_2$ (461.34).
Calcd.: C=46.68 H = 2.18 N = 18.22 S=13.90 Found: C=46.64 H = 2.16 N = 18.20 S=13.81

4-(2,3-Dichlorophenyl)-2-[6-phenyl-1,2,4-triazol[3,4-b][1,3,4-thiadiazin-3-yl]methyl)- phthalazin-1-(2*H*)-one 18 .
A mixture of aminotriazole **12** (0.02 mole) and phenacyl bromide (0.02mole)was refluxed in absolute ethanol (20ml) for 8 hours. After cooling, the reaction mixture was neutralized with ammonium hydroxide; the precipitate was collected by filtration, washed with water and crystallized from ethanol.
M.P. 210^{o}C, yield 40 %. Analysis: $C_{25}H_{18}Cl_2N_6OS$ (521.34).
Calcd.: C= 57.59 H = 3.48 N = 16.12 S=6.15 Found: C= 57.55 H = 3.44 N = 16.10 S=6.11

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