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Meldrum's acid in heterocyclic synthesis: azoles incorporating a 2,4-dichlorophenoxy moiety with anticipated molluscicidal activity

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Abstract Synthesis of the title ring system is described using ethyl 4-(2,4-dichlorophenoxy)-3-oxobutanoate as starting material. The latter was prepared through acylating *Meldrum*'s acid with the phenoxy acid chloride derivative.

Keywords *Meldrum*'s acid; Acylation; 2,4-Dichlorophenoxyacetic acid; Molluscicides.

Introduction

Search for new molluscicides is of continuous interest as bilharziosis, which still is considered an endemic disease in Egypt. In our previous work, several azoles were proved to exhibit molluscicidal activity [1–4]. Meantime, 2,4-dichlorophenoxy (2,4-*D*) moiety showed herbicidal activity [5]. So, it seemed a good idea to prepare new azoles carrying the 2,4-*D* moiety hoping to synergize both activities, for competing snails and the hyacinth plant, which have many disadvantages: it is considered a biological shelter for the infected snails that aggravates the problem, helps in the evaporation and consumption of huge amounts of water beside obstructing the navigation in the river Nile.

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Results and discussion

Ethyl 4-(2,4-dichlorophenoxy)-3-oxo-butanoate (**4**) seemed to be a suitable precursor to obtain the aimed heterocycles. It was prepared by acylating *Meldrum*'s acid **2** with 2,4-dichlorophenoxyacetyl chloride (**1**) to give the acylated *Meldrum*'s acid **3**. The chemical behavior of **3** was in accordance with its structure.

Thus, a β-ketoester synthesis is achieved after refluxing compound **3** in absolute ethanol to afford the aimed acetate **4**. Its ^{1}H NMR spectrum revealed the ethyl residue at $\delta = 4.3$ (CH_2-) and 1.3 (CH_3-) ppm. This procedure proved to be superior to the conventional β-ketoester synthesis [6].

In addition, the β-ketoester **4** was treated with phenylhydrazine in acetic acid, a new product was formed showing the molecular ion peak at m/z (M^+, 334). Its ^{1}H NMR pattern lacked the ester group protons-present in the parent **4** and showed instead a new signal at $\delta = 3.75$ ppm (2H) beside a multiplet attributable to the phenyl protons. Accordingly, the pyrazolone structure **5** was assigned to this product.

On applying a *Claisen* condensation to the pyrazolone **5**, using ethyl formate in presence of sodium ethoxide, the corresponding 3-[(2,4-dichlorophenoxy)methyl)]-5-hydroxy-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**6a**) was obtained. The detection of the hydroxymethylene proton at $\delta = 8.20$ ppm [7], suggested the prescence of **6a** principally, as hydroxyl methylene tautomer.

The pyrazolone **5** was also subjected to a *Vilsmeier-Haack* chloroformylation [8]. The product was identified as 5-chloro-3-[(2,4-dichlorophenoxy)methyl)]-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**6b**). Its mass spectrum was in accordance with its molecular formula ($C_{17}H_{11}N_2O_2Cl_3$), along with a singlet proton at $\delta = 10.0$ ppm (formyl-H).

On treating compound **6b** with sodium azide in *DMSO* in the dark, 5-azido derivative **7** was obtained (*cf.* Experimental). This nucleophilic aromatic substitution proceeded smoothly probably due to the presence of the electron withdrawing formyl substituent in the *o*-position [9].

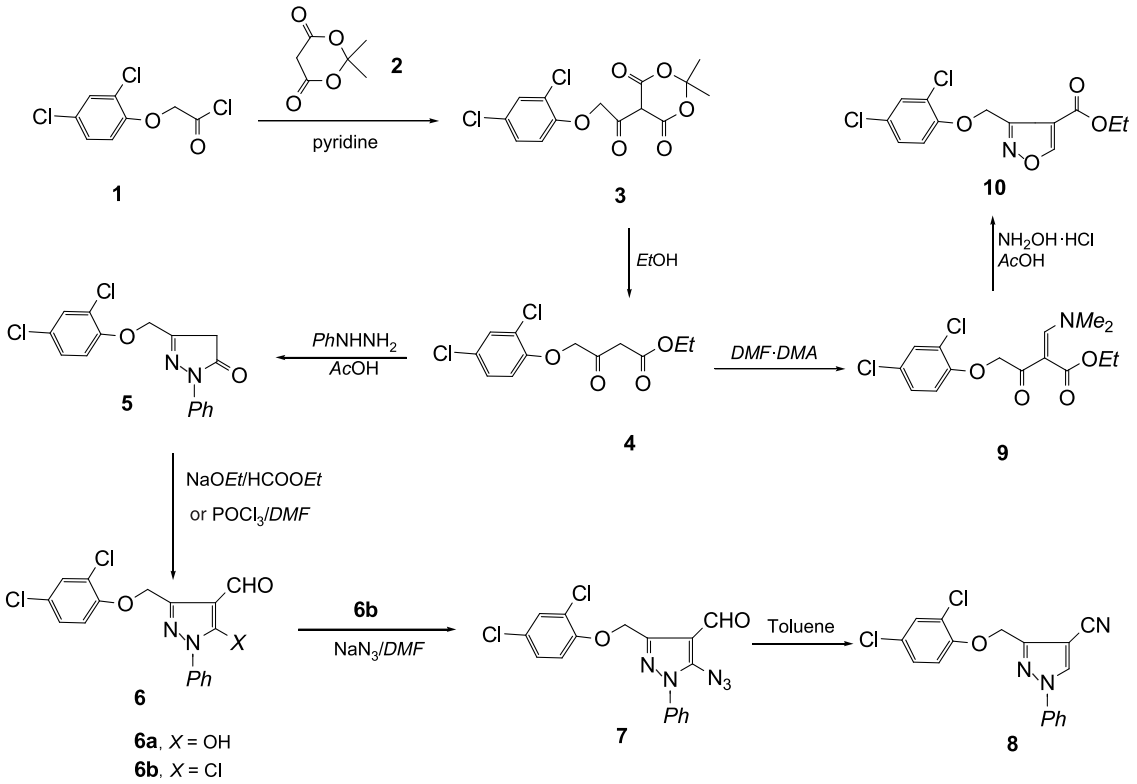
When the azide **7** was subjected to thermolysis by heating in toluene, the reaction afforded a sole product showing only an IR CN absorption and lacking the aldehydic CO. Meantime, a new singlet was detected in the latter at $\delta = 7.7$ ppm (1H). Based on these data, structure **8** was given to this product. This result does not go along with a previous reports [10–12], that when the azide group was *ortho* to an aldehyde group in a pyrazole ring, the latter could be rearranged to a furan ring when subjected to thermolysis.

Treatment of compound **4** with *N*,*N*-dimethylformamide dimethylacetal (*DMF*/*DMA*) in benzene afforded the corresponding enaminone derivative **9**. This structure assignment was based on microanalytical and spectral data. So, its ^{1}H NMR spectrum showed the *N*,*N*-dimethyl group protons at $\delta =$ 3.4 ppm together to the ylidene proton at $\delta = 7.90$ ppm.

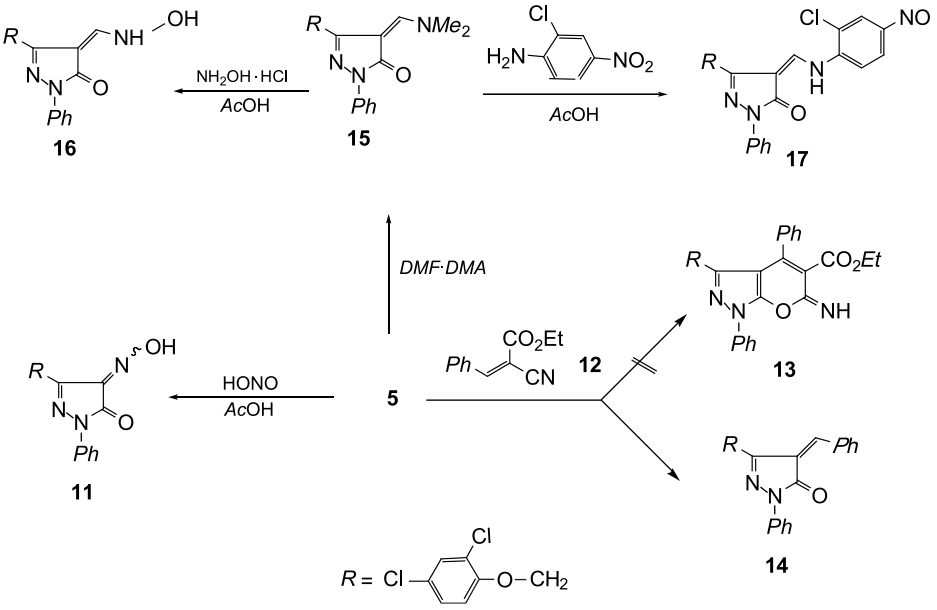
Conversion of compound **9** to isoxazole derivative **10** was successfully achieved upon its treatment with hydroxylamine hydrochloride in acetic acid. Its mass spectral data revealed the molecular ion peak at m/z (M^+, 315) while the isoxazole H-5 was detected at $\delta = 9.07$ ppm. This formation probably proceeded through the self cyclization of an initial oximino intermediate with subsequent loss of dimethylamine to yield **10** (*cf.* Scheme 1).

When the pyrazolone derivative **5** reacted with sodium nitrite in the presence of acetic acid, 4-hydroximino derivative **11** was obtained. It showed the hydroxyl proton as a (D_2O exchangeable) singlet at $\delta = 7.6$ ppm instead of the pyrazolone CH_2 protons signal-previously detected in the parent.

The pyrazolone **5** also reacted with the benzylidene ethylcyanoacetate **12** with the formation of a new product showing IR CO absorption at 1660 cm^{-1}. Its mass spectral data revealed the molecular ion peak at m/z (M^+, 422), while it is ^{1}H NMR spectrum



Scheme 1



Scheme 2

showed beside two phenyl moieties, a new singlet (1H) at $\delta = 7.94$ ppm. Based on these spectroscopic data, structure **14** is proposed instead of the expected pyrazoloiminopyran structure **13**, compound **14** probably formed *via* ylidene exchange [13].

Moreover, compound **5** was added to *N*,*N*-dimethylformamide dimethylacetal in toluene to yield the 4-dimethylaminomethylene derivative **15** the structure of which was deduced through microanalytical and spectral data (*cf.* Experimental).

In contrast to the result previously obtained with compound **9**, when compound **15** was treated with hydroxylamine hydrochloride, a nucleophilic substitution of the dimethylamino group occurred to yield compound **16**. The ^{1}H NMR of the latter showed (D_2O exchangeable) broad singnal at $\delta = 3.75$ ppm attributable to the NH and OH group protons, respectively, with absence of the dimethylamino group protons present in **15**.

Compound **15** was also treated with 2-chloro-4-nitro-aniline in acetic acid: the formed product **17** showed the molecular peak at m/z (M^+, 517) equivalent to the sum of both reactants minus a dimethylamino moiety. Accordingly, structure of compound **17** was given to this product which was also confirmed from the other elemental and spectral data (*cf.* Scheme 2).

The preliminary molluscicidal testing showed that compounds **5**, **15**, and **11** are the most promising. Further work is in progress and will be published elsewhere.

Experimental

Melting points were determined on an Electrothermal 9100 digital melting point apparatus IR, NMR, and mass spectra were recorded on Pye-Unicam SP-1100, Jeol 270 MHz and Jeol 500 MHz, with internal standard tetramethylsilane (*TMS*), and Jeol JMS-AX500. Elemental analysis (in accord with the calculated values) were carried out in the microanalytical unit, Faculty of Science, Cairo University. Precoated silica gel 60 F_{254} plates with a layer thickness 0.25 nm from Merck were used for thin layer chromatography. Yields are not optimized.

5-[2-(2,4-Dichlorophenoxy)acetyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**3**, $C_{14}H_{12}O_6Cl_2$)

To a solution of 1.44 g **2** (10 mmol) in 10 cm^3 methylene chloride in a 250 cm^3 round-bottomed flask, equipped with an addition funnel and nitrogen inlet and cooled to 0°C, pyridine (2.5 cm^3) was dropped for a period of 10 min followed by the addition of a freshly prepared solution of 2.39 g 2,4-dichlorophenoxy acetyl chloride **1** (10 mmol) in 15 cm^3 methylene chloride, which resulted in an orange solution. After complete addition (~2 h), the resulting dark orange solution was stirred for an additional hour. The solution was diluted with methylene chloride (10 cm^3) and poured onto 2 *M* HCl and ice. The two phases were separated, and the aqueous phase was extracted with methylene chloride (2×50 cm^3). The combined organic phases were washed with 2 *M* HCl (2×50 cm^3), dried over anhydrous sodium sulphate, and evaporated. The resulting organic oil was solidified with pet. ether 40–60°C, collected, washed with ether, and crystallized to give

3 (75%) as pale yellow crystals. Mp 112–113°C (toluene); IR (film): $\bar{\nu} = 3009$ (CH), 1735 (CO), 1660 (CO) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 1.79$ (s, 6H, $2 \times CH_3$), 4.0 (s, 1H, CH–), 5.10 (s, 2H, CH_2), 7.13–7.49 (m, 3H, *Ar*–H) ppm; MS: m/z (%) = 346 [M^+].

Ethyl-4-(2,4-dichlorophenoxy)-3-oxobutanoate
(**4**, $C_{12}H_{12}O_4Cl_2$)
A solution of 3.47 g **3** (10 mmol) in 50 cm^3 anhydrous ethanol was refluxed for 2.5 h. The solvent was removed *in vacuo*, leading to a dark oil which was purified by column chromatography (silica gel, ethyl acetate/pet. ether 1/2, $R_f = 0.4$) to give **4** (55%) as pale yellow needles. Mp 48–50°C; IR (film): $\bar{\nu} = 1725$ (COO*Et*), 1665 (CO) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.3$ (t, 3H, CH_3), 3.75 (s, 2H, CH_2–), 4.3 (q, 2H, CH_2-ester), 4.75 (s, 2H, CH_2-phenoxy), 6.8 (d, 1H, *Ar*–H), 7.25 (dd, 1H, *Ar*–H), 7.45 (d, 1H, *Ar*–H) ppm; MS: m/z (%) = 290 [M^+].

*Preparation of compounds **9** and **15**. General procedure*
A mixture of each **4** or **5** (10 mmol) and 1.19 g *N*,*N*-dimethyl formamide dimethyl acetal (10 mmol) in 20 cm^3 dry benzene was refluxed for 3 h. A solid product precipitated after concentration, it was filtered off, washed with petroleum ether, and finally crystallized to afford **9** or **15**.

Ethyl-4-(2,4-dichlorophenoxy)-2-[(dimethylamino)-methylene]-3-oxobutanoate (**9**, $C_{15}H_{17}NO_4Cl_2$)
Pale yellow needless, yield (65%), mp 71–73°C (ethanol); IR (film): $\bar{\nu} = 1730$ (COO*Et*), 1665 (CO), 1613 (C=C) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 1.25$ (t, 3H, CH_3-ester), 3.4 (s, 6H, N $(CH_3)_2$), 4.15 (q, 2H, CH_2-ester), 5.15 (s, 2H, CH_2–), 6.9 (d, 1H, *Ar*–H), 7.35 (dd, 1H, *Ar*–H), 7.55 (d, 1H, *Ar*–H), 7.90 (s, 1H, =CH) ppm; MS: m/z (%) = 345 [M^+].

3-[(2,4-Dichlorophenoxy)methyl]-4-[(dimethylamino)methylene]-1-phenyl-1,5-dihydropyrazol-5-one (**15**, $C_{19}H_{17}N_3O_2Cl_2$)
Pale yellow needless, yield (60%), mp 71–73°C (ethanol); IR (film): $\bar{\nu} = 1688$ (CO), 1600 (C=N) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 2.90$ (s, 6H, $N(CH_3)_2$), 5.4 (s, 2H, CH_2), 7.13–8.00 (m, 9H, *Ar*–H, C=CHN) ppm; MS: m/z (%) = 389 [M^+].

*Preparation of compounds **10** and **16**. General procedure*
A mixture of each of compounds **9** or **15** (10 mmol) and 0.69 g hydroxylamine hydrochloride (10 mmol) in 20 cm^3 acetic acid was refluxed for 1½ h. A solid that precipitated on hot was filtered off, washed with 20 cm^3 water, dried, and finally crystallized to afford **10** or **16**.

Ethyl-3-[(2,4-dichlorophenoxy)methyl]isoxazole-4-carboxylate (**10**, $C_{13}H_{11}NO_4Cl_2$)
Colorless crystals, yield (70%), mp 55–57°C (*DMF*); IR (film): $\bar{\nu} = 1720$ (CO), 1590 (C=N) cm^{-1}; ^1H NMR (500 MHz, *DMSO*-d_6): $\delta = 1.25$ (t, 3H, CH_3–), 4.27 (q, 2H, CH_2-ester), 5.66 (s, 2H, CH_2–), 7.15 (d, 1H, *Ar*–H), 7.28 (dd, 1H, *Ar*–H), 7.61 (d, 1H, *Ar*–H), 9.07 (s, 1H, isoxazole H-5) ppm; MS: m/z (%) = 315 [M^+].

3-[(2,4-Dichlorophenoxy)methyl]-4-[(hydroxyamino)-methylene]-1-phenyl-1,5-dihydropyrazol-5-one
(**16**, $C_{17}H_{13}N_3O_3Cl_2$)
Colorless crystals, yield (65%), mp 192–194°C (*DMF*); IR (film): $\bar{\nu} = 3420$ (OH), 3115 (NH), 1720 (CO), 1590 (C=N) cm^{-1}; ^1H NMR (500 MHz, *DMSO*-d_6): $\delta = 3.75$ (brs, 2H, OH, NH), 5.17 (s, 2H, OCH_2–), 7.70–7.56 (m, 9H, *Ar*–H, =CH) ppm; MS: m/z (%) = 378 [M^+].

3-[(2,4-Dichlorophenoxy)methyl]-1-phenyl-1,5-dihydro-pyrazol-5-one (**5**, $C_{16}H_{12}N_2O_2Cl_2$)
To a stirred solution of compound 2.9 g **4** (10 mmol) in 20 cm^3 acetic acid, 1.08 cm^3 phenyl hydrazine (10 mmol) was added dropwise within 15 min. After the addition was completed, the reaction mixture was stirred at room temperature for another 2 h. A solid product precipitated during stirring, it was filtered off, washed with hot water (20 cm^3), dried, and crystallized to give **5** (75% yield) as pale brown crystals. Mp 179–181°C (acetic acid); IR (film): $\bar{\nu} = 1693$ (CO), 1599 (C=N) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 3.75$ (s, 2H, CH_2 pyrazolone), 5.0 (s, 2H, CH_2), 7.0–7.90 (m, 8H, *Ar*–H) ppm; MS: m/z (%) = 334 [M^+].

3-[(2,4-Dichlorophenoxy)methyl)]-5-hydroxy-1-phenyl-1H-pyrazole-4-carbaldehyde (**6a**, $C_{17}H_{12}N_2O_3Cl_2$)
To a solution of 3.35 g **5** (10 mmol) in ethyl formate (30 cm^3), sodium sand (10 mmol) was added (prepared by refluxing sodium metal in toluene) over a water bath. After 5 min, ethanol (2 drops) was added to the reaction mixture to activate it and the reflux was continued for 4 h. After a compact mass was formed, 10 cm^3 ethanol were added to it to get rid of the residual sodium, it was poured over crushed ice, and finally acidified with HCl. A precipitate separated out, it was filtered off and crystallized to give **6a** (50% yield) as yellow crystal. Mp 218–220°C (ethanol); IR (film): $\bar{\nu} = 3400$ (OH), 1630 (CO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.30$ (s, 2H, CH_2O–), 7.27–7.80 (m, 8H, *Ar*–H), 8.20 (s, 1H, =CHOH) ppm; MS: m/z (%) = 363 [M^+].

5-Chloro-3-[(2,4-dichlorophenoxy)methyl)]-1-phenyl-1H-pyrazole-4-carbaldehyde (**6b**, $C_{17}H_{11}N_2O_2Cl_3$)
To 0.73 g dry *DMF* (10 mmol) cooled to 0°C, 2 cm^3 $POCl_3$ (13 mmol) were slowly added at such a rate that the temperature was maintained below 10°C followed by the addition of 3.35 g **5** (10 mmol) in small portions. The resulting solution was stirred at room temperature for 30 min and at 50°C for 1 h. The dark reaction mixture was then cooled to room temperature and poured slowly onto ice/H_2O and neutralized to *pH* 6–7 by adding Na_2CO_3 in small portions. The resulting brown solid was filtered off, washed with 50 cm^3 water, and crystallized to afford **6b** (55% yield) as yellow crystals. Mp 100–102°C (ethanol); IR (film): $\bar{\nu} = 1680$ (CHO), 1523 (C=N) cm^{-1}; ^1H NMR (500 MHz, *DMSO*-d_6): $\delta = 5.42$ (s, 2H, CH_2), 7.36–7.62 (m, 8H, *Ar*–H), 10.0 (s, 1H, CHO) ppm; MS: m/z (%) = 380 [M^+].

5-Azido-3-[(2,4-dichlorophenoxy)methyl)]-1-phenyl-1H-pyrazole-4-carbaldehyde (**7**, $C_{17}H_{11}N_5O_2Cl_2$)
To a solution of 3.8 g **6b** (10 mmol) in 25 cm^3 *DMSO*, 0.65 g sodium azide (10 mmol) were added and the reaction mixture was stirred for 48 h at 35°C in the absence of light. The solution was diluted with H_2O (100 cm^3) and extracted with Et_2O (3×50 cm^3). The organic phase was washed with H_2O (100 cm^3), after which it was dried (Na_2SO_4). Removal of the solvent left a solid residue, which was purified by column chromatography (silica gel, *Ac*O*Et*/pet. ether, 1/3, $R_f = 0.35$) to give **7** (60% yield) as colorless crystals. Mp 117–118°C; IR (film): $\bar{\nu} = 2136$ (azido group), 1662 (CO), 1586 (C=N) cm^{-1}; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 5.47$ (s, 2H, CH_2), 7.41–7.65 (m, 8H, *Ar*–H), 10.06 (s, 1H, CHO) ppm; MS: m/z (%) = 388 [M^+].

3-[(2,4-Dichlorophenoxy)methyl]-1-phenyl-1H-pyrazole-4-carbonitrile (**8**, $C_{17}H_{11}N_3OCl_2$)
Compound **7** (3.88 g, 10 mmol) was dissolved in 50 cm^3 toluene in an atmosphere of dry N_2 and stirred at 100°C. After 5 h, the reaction mixture was cooled to room temperature, and the toluene was removed *in vacuo*. The resulting oil was chromatographed (silica gel, *Ac*O*Et*/pet.ether, 1/1, $R_f =$ 0.25) to afford **8** (55% yield) as a pale yellow crystals. Mp 212–214°C; IR (film): $\bar{\nu} = 2252$ (CN), 1595 (C=N) cm^{-1}; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 5.18$ (s, 2H, CH_2), 7.48–7.59 (m, 8H, *Ar*–H), 7.70 (s, 1H, pyrazole H-5) ppm; MS: m/z (%) = 343 [M^+].

3-[(2,4-Dichlorophenoxy)methyl]-4-(hydroxyimino)-1-phenyl-1,5-dihydropyrazol-5-one (**11**, $C_{16}H_{11}N_3O_3Cl_2$)
To a solution of 3.35 g **5** (10 mmol) in 20 cm^3 acetic acid, aqueous sodium nitrite (20 mmol) was added portionwise, with stirring at 0–5°C, over a period of 20 min. After 1½ h, the reaction mixture was poured onto water, a precipitate was formed, filtered off, and crystallized to give **11** (65% yield) as orange yellow crystal. Mp 171–173°C (ethanol); IR (film): $\bar{\nu} = 3400$ (OH), 1650 (CO), 1611 (C=N) cm^{-1}; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 5.3$ (s, 2H, CH_2), 7.33–7.73 (m, 9H, 8*Ar*–H, OH) ppm; MS: m/z (%) = 363 [M^+].

3-[(2,4-Dichlorophenoxy)methyl]-4-[benzylidene]-1-phenyl-1,5-dihydro pyrazole-5-carboxylate (**14**, $C_{23}H_{16}N_2O_2Cl_2$)
A mixture of 3.35 g **5** (10 mmol) and 2.0 g benzylidene ethylcyanoacetate **12** (10 mmol) in 30 cm^3 ethanol in presence of triethylamine (3 drops) was refluxed for 5 h. A precipitate which was formed on hot, filtered off while hot, and crystallized to give **14** (70% yield) as pale yellow crystals. Mp 200–201°C (acetic acid); IR (film): $\bar{\nu} = 1605$ (C=C), 1660 (CO) cm^{-1}; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 4.9$ (s, 2H, CH_2–), 7.15–7.40 (m, 13H, *Ar*–H), 7.94 (s, 1H, =CH *Ph*) ppm; MS: m/z (%) = 422 [M^+].

4-[(2-Chloro-4-nitrophenylamino)methylene]-3-[(2,4-dichlorophenoxy)methyl]-1-phenyl-1,5-dihydropyrazol-5-one (**17**, $C_{23}H_{15}N_4O_4Cl_3$)
A mixture of 3.9 g **15** (10 mmol) and 1.72 g 2-chloro-4-nitroaniline (10 mmol) in 25 cm^3 acetic acid was refluxed for 3 h. A precipitate which was formed on hot, filtered off, and crystallized to give **17** (70% yield) as orange crystals. Mp 241–243°C (*DMF*); IR (film): $\bar{\nu} = 3110$ (NH), 1670 (CO) cm^{-1}; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 5.31$ (s, 2H, OCH_2–), 7.41–8.48 (m, 11H, *Ar*–H), 8.49 (s, 1H, =CH), 9.05 (s, 1H, NH) ppm; MS: m/z (%) = 517 [M^+].

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