Synthesis of polyfunctional substituted pyrazoles

Mohamed F. El-Shehry, Emad M. El-Telbani* and Randa H.Swellem

Green Chemistry Department, National Research Centre, Dokki 12622, Cairo, Egypt

Synthesis of pyrazoles incorporating substituted derivatives of 2, 4-dichloroacetic acid residues is described. Reactions with different reagents afford fused and polyfunctional substituted pyrazoles.

Keywords: β-ketoester, pyrazole, pyran, oxime

Pyrazole derivatives have received more and more attention in the recent years. Pharmaceutical research into such compounds has been reported, including a potent cyclin dependent kinase 1 (CDK1) inhibitors,[1] HIV reverse transcriptase inhibitors,[2] CCR1 antagonists,[3] protein kinase inhibitors[4] and inhibitors of cGMP degradation. In addition, they show a wide range of pharmacological activities[5,6] together with several herbicidal, fungicidal[7] and molluscicidal activities.[8] Recently, we reported a simple and versatile route for preparing a new β-ketoester **1** starting from 2, 4-dichlorophenoxyacetic acid which possesses an excellent herbicidal activity.[9] This reaction is widely applicable for the preparation of different substituted heterocyclic compounds having a 2, 4-D residue as possible molluscicidal agents.[8] In an effort to extend the scope of this method, we attempted to prepare further interesting bioactive compounds having 2, 4-D residue, which may show potential pharmaceutical activities in addition to molluscicidal and herbicidal activities.

Results and discussion

We successfully transformed ethyl-4-(2, 4-dichlorophenoxy)-3-oxo-butanoate (**1**) which was recently prepared by us in high yield[8] into 3-((2, 4-dichlorophenoxy) methyl)-2, 4-dihydopyrazol-5-one (**2a**) through reaction with hydrazine hydrate in the presence of an acidic medium. Also, 3-((2, 4-dichlorophenoxy) methyl)-1-phenyl-1, 5-dihydropyrazol-5-one **(2b**) was prepared when, **1** was treated with phenyl hydrazine in the presence of acetic acid.[8] Compound **2a** showed in its ^{1}H NMR spectrum a new methylene protons signal at δ = 5.50 ppm characteristic for the pyrazolone CH_2-protons. Moreover, the ^{13}C NMR revealed a signal at δ = 152.87 ppm attributed to the pyrazolone CO.

Compound **2a** was nitrosated with sodium nitrite in acetic acid to give the corresponding oxime **3a**. Its mass spectrum showed at *m/z* = 288, which was in accord with the calculated molecular weight $C_{10}H_7Cl_2N_3O_3$. ^{1}H NMR showed the hydroximino proton as a broad singlet at δ = 7.70 ppm as (D_2O exchangeable), along with the other protons at their expected locations. Compound **2a** was also coupled with the diazonium salt of aniline, affording the phenylazo derivative **3b** in moderate yield. Its ^{1}H NMR spectrum showed two (D_2O exchangeable) at δ = 9.05 and 10.11 ppm assigned to both NH groups, while the M^+ was detected at *m/z* = 362.

Compound **2a** was condensed with anisaldehyde in the presence of triethylamine as catalyst to give the condensed product **3c**. Both elemental and spectroscopic data was in accord with the suggested structure **3c**. ^{1}H NMR showed a new ylidene CH-proton at δ = 8.70 ppm with a disappearance of the pyrazolone CH_2 proton detected in the parent **2a**. Upon treating **3c** with hydrazine hydrate in ethanol, the corresponding pyrazolopyrazole derivative **4** was obtained in low yield. The mass spectrum of compound **4** showed at *m/z* = 388 while, the ^{1}H NMR spectrum revealed a new NH signal at δ = 10.30 ppm with a lack of the peak attributed to the ylidine proton detected in the parent **3c**.

Furthermore, **2a** reacted with phosphoryl chloride in dimethyl formamide under Vilsmier–Haack chloroformylation conditions to afford the pyrazol-4-carbaldehyde derivative **5** in good yield. The ^{1}H NMR spectrum of **5** revealed a signal at δ = 8.45 ppm characteristic for the aldehydic proton.[8,10] Moreover, ^{13}C NMR revealed a signal at δ = 183.70 ppm characteristic for the aldehydic CHO group.

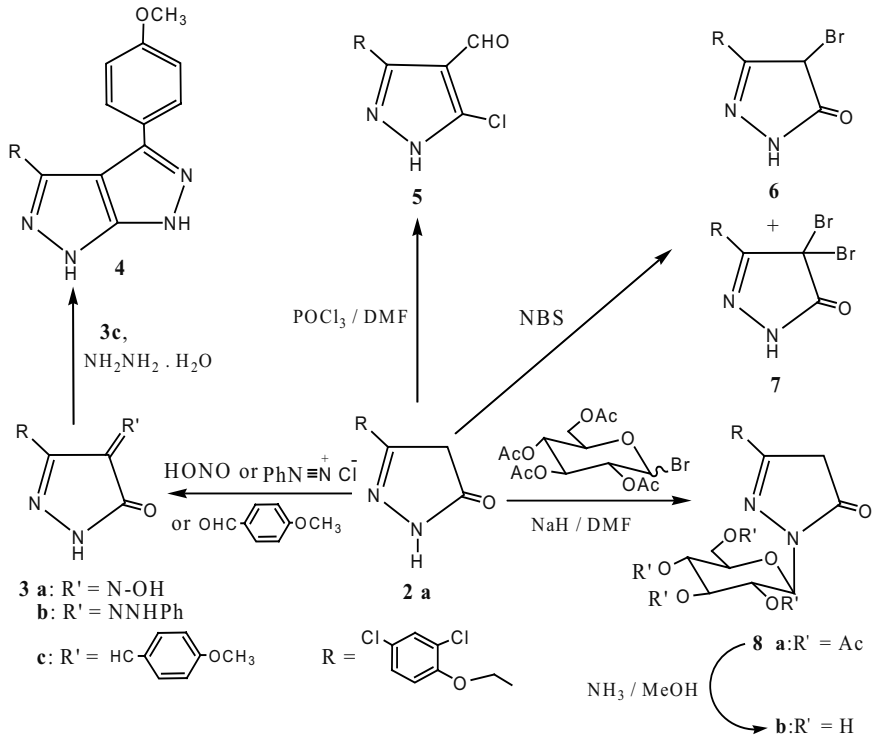
Bromonation of **2a** with *N*-bromosuccinimide (NBS) in chloroform afforded two isolable products 4-bromopyrazol-3-one **6** and the 4, 4-dibromo derivativese **7** in 2 : 1 ratio. Structures **6** and **7** were based on both spectral and microanalytical data, ^{1}H NMR of **6** revealed a signal at δ = 5.25 ppm (one proton), attributed to the pyrazolone H-4 with disappearance of the signal at δ = 5.50 ppm (two protons) characteristic for the pyrazolone CH_2 protons. Moreover, the mass spectrum was in accord with the proposed structure. On the other hand, the mass spectrum of **7** showed at *m/z* = 417 which was in accord with the calculated molecular weight ($C_{10}H_6Br_2Cl_2N_2O_2$), while, the ^{1}H and ^{13}C NMR supported the suggested dibromo structure **7** (*cf*. Experimental).

From a biological view, it seemed a good idea to form the *N*-glucosylated derivative of the pyrazolone **2a** to enhance its solubility thereby enhancing the rate of adsorption. To this purpose, **2a** was coupled with 2, 3, 4, 6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in dimethylformamide in the presence of sodium hydride to yield the *N*-glucoside derivative **8a**. The ^{1}H NMR of **8a** revealed the absence of the NH and presence of the all protons characteristic for the tetraacetyl glucose moiety (*cf*. Experimental). Deprotection of the tetraacetyl groups of **8a** could be achieved by passing ammonia into the methanolic solution of **8a** to give the deprotected product **8b**. (*cf*. Scheme 1).

Acetylation of **2a** and **2b** using acetyl chloride in dioxane in the presence of calcium hydroxide, gave the acetylated products **9a** and **9b**, respectively. Both elemental and spectroscopic data of **9a** and **9b** supported the suggested structures. The ^{1}H NMR of **9a** revealed the presence of two acetyl groups at δ = 2.20 and 2.36 ppm and the pyrazolone 4-H at δ = 6.37 ppm with a lack of the pyrazole CH_2 protons detected in the parent **2a**, and the ^{13}C NMR revealed a signal at δ = 167.80 and 170.32 ppm attributed to two acetyl CO groups. Moreover, the mass spectrum was in accord with the calculated molecular weight ($C_{14}H_{12}Cl_2N_2O_4$).The ^{1}H NMR of **9b** showed a signal at δ = 2.23 ppm attributed to the $COCH_3$ protons with **la** ack of the pyrazole CH_2 detected in the parent **2b**. Moreover, its mass spectrum was in accord with the calculated molecular weight ($C_{18}H_{14}Cl_2N_2O_3$).

Better success was achieved in synthesising a fused bicyclic compounds with 2, 4-dichlorophenoxy residue using **9b** as a synthon. To this aim, **9b** was reacted with benzaldehyde in the presence of methanolic potassium hydroxide to give **10** in moderate yield. In the ^{1}H NMR of **10** appeared new doublet signals at δ = 7.40 and 7.80 ppm characteristic for the olefenic double bond with a lack of the acetyl proton detected in the parent **9b**. Furthermore, **10** was cyclised using piperidine in

* Correspondent. E-mail: e_misbah@yahoo.co.uk



Scheme 1

boiling ethanol to afford the pyranopyrazole derivative **11**. The IR spectrum of **11** revealed a new CO group at 1685 cm^{-1} while the ^1H NMR showed a new singlet peak at δ = 5.60 ppm characteristic of a pyran H-2 [11] with disappearance of olefinic protons detected in the parent **10**.

9b was reacted with acetone in the presence of pyrrolidine using a Dean–Stark apparatus to afford the pyranopyrazole derivative **12** in a moderate yield. The IR spectrum showed the pyranone CO group at 1670 cm^{-1} and the ^1H NMR spectrum showed a characteristic singlet peak at δ = 3.80 ppm for the $COCH_2$ group[12] (*cf*. Experimental and Scheme 2)

When the reaction of **2a** with anisaldehyde was carried out in the presence of an excess of triethylamine another product **13a** was obtained. **13a** might be formed through formation of **3c** followed by addition of another molecule of **2a** and finally by subsequent elimination of a molecule of water to give the pyran derivative **13a**. The mass spectrum of **13a** showed at *m/z* = 617 which is in accord with the calculated molecular weight and its ^1H NMR revealed a new signal at δ = 4.80 ppm characteristic for the pyran H-4.[13]

Similarly, when compound **2a** was reacted with benzaldehyde in the presence of an excess of triethylamine the same previous result was obtained whereby the pyran derivative **13b** afforded directly without isolation the condensed adduct. The ^1H NMR of **13b** showed the pyran H-4 proton at δ = 4.90 ppm, which supported the suggested structure **13b**.

To elucidate the mechanism of the reaction pathway, the same reaction was performed on another substituted *N*-phenyl pyrazolone namely, 3-(2, 4-dichlorophenoxymethyl)-1-phenyl-1, 5-dihydropyrazol-5-one (**2b**) under the same reaction conditions. In a similar manner, the substituted pyran derivative **13c** was obtained as a complex with a molecule of water[14] (*cf*. Experimental).

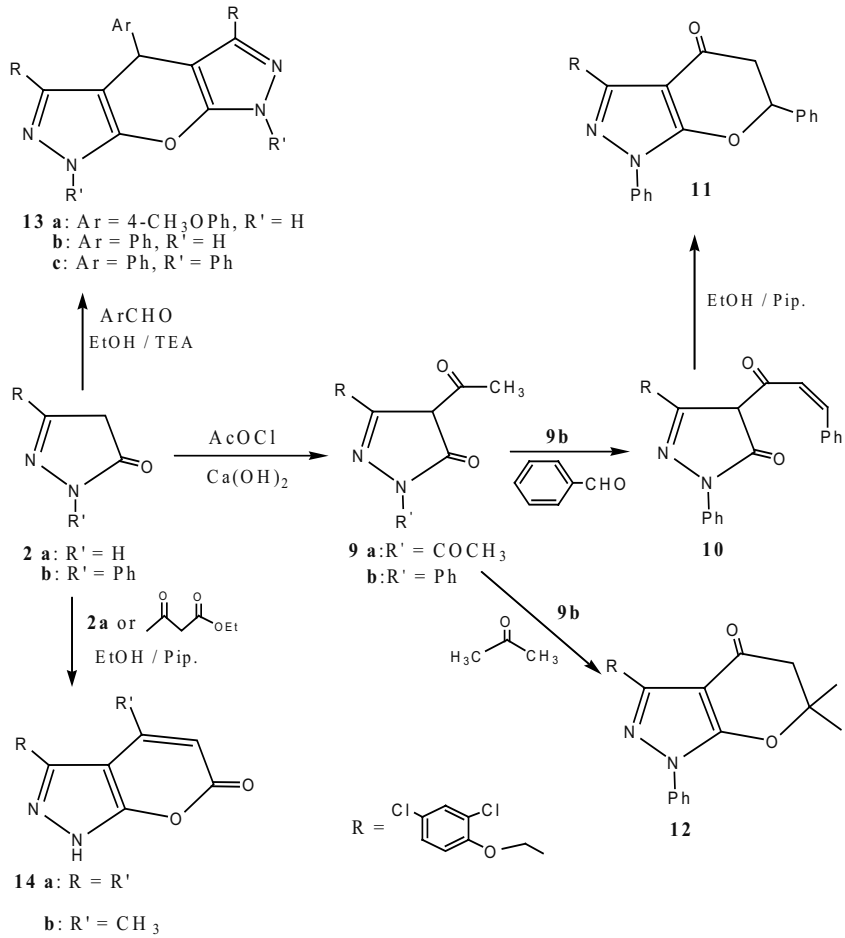
Compound **2a** was condensed with some β-ketoesters namely, ethyl-4-(2, 4-dichlorophenoxy)-3-oxo-butanoate (**1**) or ethyl acetoacetate in the presence of a basic medium to yield the corresponding compounds **14a** and **14b** in good yields, respectively. All elemental and spectral data of compounds **14a** and **14b** were in accord with the suggested structures. The ^1H NMR of compound **14a** as a representative example showed a coumarin H-5 at δ = 5.80 ppm with the disappearance of the CH_2 of pyrazole detected in the parent **2a**. Moreover, the ^{13}C NMR showed the coumarin CO at δ = 170.55 ppm and the mass spectrum showed *m/z* = 486, which was in accord with the calculated molecular weight ($C_{20}H_{12}Cl_4N_2O_4$) (*cf* Experimental). Biological activities of products will be studied.

Experimental

Melting points were determined on an Electrothermal 9100 digital melting point apparatus. IR, NMR and mass spectra were recorded on: IR spectra (KBr): Pye-Unicam SP-1100. ^1H, ^{13}C NMR spectra: Bruker AMX400 MHz, Jeol 500 and Jeol GLM EX 270 MHz FT NMR spectrophotometer, DMSO-d_6, TMS as internal standard, chemical shift in δ (ppm). Mass spectra: 70 eV, Varian MAT 311 A. 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 optimised.

5-((2, 4-Dichlorophenoxy) methyl)-2, 4-dihydropyrazol-3-one **(2a)**: To a solution of **1** (2.90 g, 10 mmol) in acetic acid (20 mL), hydrazine hydrate (0.75 g, 15 mmol) was added dropwise within 30 min. After the addition was completed, the reaction mixture was stirred at room temperature; for another 3 h. A solid product precipitated during stirring was filtered off, washed with hot water (20 mL), dried and recrystallised from ethanol to give **2a** as a white solid, m.p.168–170 °C; (2 g, 77% yield). IR (KBr): ν_{max} 3360 (NH), 1693 (CO), 1599 (C=N)cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 4.90 (s, 2H, CH_2 phenoxy), 5.50 (s, 2H, CH_2), 7.10–7.70 (m, 3H, ArH), 10.55 (s, 1H, NH) ppm. ^{13}C NMR (400 MHz, DMSO-d_6): δ 63.48, 89.54, 115.89, 122.93, 125.14, 128.37, 129.71, 152. 87. MS: *m/z* (%) = 259 (5%) [M^+]. Anal. Calcd for $C_{10}H_8Cl_2N_2O_2$ (259.18): C, 46.34; H, 3.11; N, 10.81. Found: C, 46.30; H, 3.20; N, 10.90%.

5-((2, 4-Dichlorophenoxy) methyl)-2H-pyrazol-3, 4-dione-4-oxime **(3a)**: To a cooled solution of compound **2a** (2.85 g, 10 mmol) in acetic acid (20 mL), aqueous sodium nitrite (1.38 g, 20 mmol) was added portionwise, with stirring at 0–5 °C, over a period of 20 min. After 2 h, the reaction mixture was poured over water and a precipitate



Scheme 2

was formed, filtered and recrystallised from acetic acid to give **3a** as a white solid, m.p. 165–167 °C; (2 g, 71% yield). ^{1}H NMR (270 MHz, DMSO-d_6): δ 5.51 (s, 2H, CH_2 phenoxy), 7.10–7.81 (m, 4H, ArH, OH), 10.10 (s, 1H, NH) ppm. MS: *m/z* (%) = 288 (6%) [M^+]. Anal. Calcd for $C_{10}H_7Cl_2N_3O_3$ (288.18): C, 41. 68; H, 2.45; N, 14.58. Found: C, 41.70; H, 2.40; N, 14.70%.

5-((2, 4-Dichlorophenoxy) methyl)-4-(phenylhydrazono)-2, 4-dihydropyrazol-3-one **(3b)**: To a stirred cooled solution of **2a** (2.85 g, 10 mmol) and sodium acetate (5.1 g, 80 mmole) in dioxane (30 mL), the diazonium salt of aniline was added and the temperature was kept at (0–5 °C) for about 1 h. After removing the ice bath, stirring was maintained for 30 min at room temperature. Then water (100 mL) was added, the precipitated was filtered off, washed with water and recrystallised from methanol to give **3b** as a white solid, m.p. 210–212 °C (1.9 g, 52% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.56 (s, 2H, CH_2 phenoxy), 7.10–7.78 (m, 8H, ArH), 9.05 (s, 1H, NH), 10.11 (s, 1H, NH) ppm. MS: *m/z* (%) = 362 (10%) [M^+ -1]. Anal. Calcd for $C_{16}H_{12}Cl_2N_4O_2$ (363.29): C, 52.91; H, 3.33; N, 15.43. Found: C, 52.80; H, 3.50; N, 15.60%.

5 – ((2, 4 – Dichlorophenoxy) methyl) – 4 – (4-methoxybenzylidene)-2, 4-dihydropyrazol-3-one **(3c)**: A mixture of **2a** (2.85 g, 10 mmol) and anisaldehyde (10 mmol) in ethanol (20 mL) in the presence of one drop of triethylamine was stirred for 1 h at 70 °C. After cooling, the separated precipitate was filtered off, washed with ethanol, dried and recrystallised from ethanol to give **3c** as yellow crystals, m.p. 176–178 °C; (1.4 g, 37% yield). ^{1}H NMR (270 MHz, DMSO-d_6): δ 3.70 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2 phenoxy), 7.00–7.90 (m, 7H, ArH), 8.70 (s, 1H, ylidene CH), 10.50 (s, 1H, NH) ppm. MS: *m/z* (%) = 377 [M^+]. Anal. Calcd for $C_{18}H_{14}Cl_2N_2O_3$ (377.32): C, 57.30; H, 3.74; N, 7.42. Found: C, 57.40; H, 3.60; N, 7.40%.

3-((2, 4-Dichlorophenoxy) methyl)-4-(4-methoxyphenyl)-1, 6-dihydro pyrazolo [3, 4-c] pyrazole **(4)**: A mixture of **3c** (3.76 g, 10 mmol) and hydrazine hydrate (0.75 g, 15 mmol) in ethanol (30 mL) was heated under reflux for 4 h, the solid precipitated after concentration was filtered off, dried and recrystallised from methanol to give **4** as a white solid, m.p. 130–132 °C; (1.2 g, 30% yield). ^{1}H NMR (270 MHz, DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2 phenoxy), 7.15–7.80 (m, 7H, ArH), 10.10 (s, 1H, NH), 10.30 (s, 1H, NH) ppm. MS: *m/z* (%) = 388 [M^+ -1]. Anal. Calcd for $C_{18}H_{14}Cl_2N_4O_2$ (389.33): C, 55.53; H, 3.62; N, 14.39. Found: C, 55.70; H, 3.70; N, 14.30%.

3-((2, 4-Dichlorophenoxy) methyl)-5-chloro-1H-pyrazole-4-carbaldehyde (**5**): To dry DMF (0.73 g, 10 mmol) cooled to 0 °C, $POCl_3$ (2 mL, 13 mmol) was slowly added at such a rate that the temperature was maintained below 10 °C followed by the addition of **2a** (2.58 g, 10 mmol) in a 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 neutralised to pH 6-7 by adding Na_2CO_3 in small portions and the resulting solid was filtered off, washed with water (50 mL) and recrystallised from ethanol to give **5** as yellow crystals, m.p. 193–195 °C; (1.89 g, 62% yield). IR (KBr): ν_{max} 3355 (NH), 1680 (CHO), 1523 (C=N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.91 (s, 2H, CH_2 phenoxy), 7.11–7.52 (m, 3H, ArH), 8.45 (s, 1H, aldehydic H), 9.55 (s, 1H, NH)) ppm. ^{13}C NMR (400 MHz, DMSO-d_6): 65.74, 104.71, 116.43, 122.9, 125.28, 128.34, 129.68, 154.05, 183.70. MS: *m/z* (%) = 304 (10%) [M^+ –1]. Anal. Calcd for $C_{11}H_7Cl_3N_2O_2$ (305.69): C, 43.22; H, 2.31; N, 9.16. Found: C, 43.30; H, 2.50; N, 9.10%.

Preparation of compounds **(6)** *and* **(7)**

To a stirred suspension of **2a** (2.58 g, 10 mmol) in anhydrous carbon tetrachloride (50 mL), *N*-bromosuccinimide (1.77 g, 10 mmol) was added in the presence of a catalytic amount of (10 mg) benzoyl peroxide. The resulting mixture was refluxed for 2.5 h. After completion, the mixture was diluted with water (30 mL), the two phases were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The organic extracts were evaporated and purified by column chromatography (silica gel, ethyl acetate/n-hexane, 1/2, R_f = 0.35) to afford **6** and **7**.

4-Bromo-5-((2, 4-dichlorophenoxy) methyl)-2, 4-dihydro-pyrazol-3-one **(6)**: Pale yellow needles, m.p. 133–135 °C; (2.1 g, 62% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.01 (s, 2H, CH_2 phenoxy), 5.25 (s, 1H, pyrazolone H-4), 7.17–7.66 (m, 3H, ArH), 11.81 (s, 1H, NH) ppm. MS: *m/z* (%) = 338 [M^+]. Anal. Calcd for $C_{10}H_7BrCl_2N_2O_2$

(338.09)*:* C, 35.52; H, 2.09; N, 8.29. Found: C, 35.60; H, 2.20; N, 8.40%.

4, 4-Dibromo-5-((2, 4-dichlorophenoxy) methyl)-2, 4-dihydropyrazol -3-one **(7)**: Yellow needles, 143–145 °C; (1.7 g, 35% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.10 (s, 2H, CH_2 phenoxy), 7.20–7.65 (m, 3H, ArH), 10.65 (s, 1H, NH) ppm. ^{13}C NMR (400 MHz, DMSO-d_6): 62.09, 116.13, 123.13, 125.53, 125.63, 128.4, 129.81, 152.79. MS: *m/z* (%) = 417 (4%) [M^+]. Anal. Calcd for $C_{10}H_6Br_2Cl_2N_2O_2$ (416.98): C, 28.80; H, 1.45; N, 6.72. Found: C, 28.70; H, 1.30; N, 6.60%.

2-(2, 3, 4, 6-Tetra-O-acetyl-β–D-glucopyranosyl)-5-((2, 4-dichlorophenoxy) methyl)-2, 4-dihydropyrazol-3-one **(8a)**: Compound **2a** (2.58 g, 10 mmol) was stirred with an equimolar amount of sodium hydride in dry dimethylformamide (25 mL) for 2 h at room temperature. To the formed salt, a solution of 2, 3, 4, 6-tetra-*O*-acetyl-α-D-gylcopyranosyl bromide (4.1 g, 10 mmole) in dimethylformamide (20 mL) was added dropwise and stirring was continued for an additional 2 h at room temperature. The reaction mixture was acidified with (50%) acetic acid, and then extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, evaporated, and the remaining oily residue was separated by column chromatography (silica gel, ethyl acetate/pet-ether, 1/3, R_f = 0.35), to give **8a** as colourless needles, m.p. 181–183 °C; (1.5 g, 31% yield). ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.80–2.00 (4 s, 12H, 4 × $COCH_3$), 3.32 (m, 1H, H-6, 6'), 3.41 (s, 2H, pyrazolone CH_2), 4.22 (m, 2H, H-4', 5'), 5.02 (m, 2H, H-3'), 5.20 (s, 2H, CH_2 phenoxy), 5.42 (m, 1H, H-2'), 5.60 (d, 1H, H-1'), 7.15–7.81 (m, 3H, ArH) ppm. Anal. Calcd for $C_{20}H_{26}Cl_2N_2O_7$ (477.43): C, 50.31; H, 5.49; N, 5.87. Found: C, 50.40; H, 5.40; N, 5.90%.

2-(2, 3, 4, 6-Tetrahydroxy-β-D-glucopyranosyl)-5-((2, 4-dichlorophenoxy) methyl)-2, 4-dihydropyrazol-3-one **(8b)**: Compound **8a** (4.76 g, 10 mmol) was dissolved in a solution of methanol saturated with ammonia (30 mL) and stirred for two days at room temperature. Then the solution was concentrated to dryness and the residue was recrystallised to yield **8b** as colourless needles, m.p. 241–243 °C; (1.6 g, 38% yield). ^{1}H NMR (270 MHz, DMSO-d_6): δ 3.11 (m, 1H, H-6, 6'), 3.80 (s, 2H, pyrazolone CH_2), 4.10–4.43 (m, 8H, H-4', H-5', H-2', H-3', 2'-OH, 3'-OH, 4'-OH, 6'-OH), 5.10 (s, 2H, CH_2 phenoxy), 5.32 (d, 1H, H-1'), 7.05-7.80 (m, 3H, ArH) ppm. Anal. Calcd for $C_{16}H_{18}Cl_2N_2O_7$ (421.23): C, 45.62; H, 4.31; N, 6.65. Found: C, 45.70; H, 4.40; N, 6.40%.

Preparation of compounds **(9a**, **b);** *general procedure*

A suspension of compound **2a** and/or **2b** (10 mmol) and calcium hydroxide powder (1.48 g, 20 mmol) in dioxane (50 mL) was stirred vigorously and treated with acetyl chloride (0.78 g, 10 mmol) over 30 min. The stirring was continued for another 1 h, and then the reaction mixture was filtered, and poured into ice-cold water and finally acidified with 2 N hydrochloric acid (25 mL). A solid product was filtered off, washed with water, and recrystallised to give **9a** or **9b**, respectively.

3-((2, 4-Dichlorophenoxy) methyl)-1, 4-diacetyl-1H-pyrazol-5(4H)-one **(9a)**: Grey needles, 145–147 °C; (2 g, 58% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, $COCH_3$), 2.36 (s, 3H, $COCH_3$), 5.51 (s, 2H, CH_2 phenoxy), 6.37 (s, 1H, pyrazolone H-4), 7.00–7.82 (m, 3H, ArH) ppm. ^{13}C NMR (400 MHz, DMSO-d_6): 20.60, 22.41, 64.33, 102.40, 115.45, 122.51, 125.20, 128.20, 129.44, 143.41, 152.14, 156.05, 167.80, 170.32. MS: *m/z* (%) = 343 (60%) [M^+]. Anal. Calcd for $C_{14}H_{12}Cl_2N_2O_4$ (343.16): C, 49.00; H, 3.52; N, 8.16. Found: C, 49.10; H, 3.50; N, 8.10%.

3-((2, 4-Dichlorophenoxy) methyl)-4-acetyl-1-phenyl-1H-pyrazol-5-(4H)-one **(9b)**: Pale yellow needles, m.p. 184–186 °C; (2.5 g, 66% yield). ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.23 (s, 3H, $COCH_3$), 5.20 (s, 2H, CH_2 phenoxy), 6.25 (s, 1H, pyrazolone H-4), 7.10–7.76 (m, 8H, ArH) ppm. MS: *m/z* (%) = 377 [M^+]. Anal. Calcd for $C_{18}H_{14}Cl_2N_2O_3$ (377.23): C, 57.31; H, 3.73; N, 7.43. Found: C, 57.40; H, 3.90; N, 7.30%.

5-((2, 4-Dichlorophenoxy) methyl)-2-phenyl-4-(3-phenylacryloyl)-4, 5-dihydro pyrazol-3-one **(10)**: To a mixture of **9b** (3.76 g, 10 mmol) in a 10% solution of sodium hydroxide (10 mL) in an ice bath, benzaldehyde was added dropwise (1.06 g, 10 mmol) within 15 min and the stirring was continued for another 1/2 hour at room temperature. The reaction mixture was poured into ice-cooled water and acidified with diluted hydrochloric acid. The yellow precipitate which was formed was filtered off, washed with water, dried and recrystallised to yield **10** as yellow needles, m.p. 163–165 °C; (2 g; 43% yield). ^{1}H NMR (270 MHz, DMSO-d_6): δ 4.80 (s, 2H, CH_2 phenoxy), 5.21 (s, 1H, pyrazolone H-4), 7.00–7.65 (m, 14H, ArH and olefinic-H), 7.80 (d, 1H, olefinic-H) ppm. MS: *m/z* (%) = 465 (5%) [M^+]. Anal. Calcd for $C_{25}H_{18}Cl_2N_2O_3$ (465.34): C, 64.53; H, 3.90; N, 6.02. Found: C, 64.60; H, 3.70; N, 6.10%.

3-((2, 4-Dichlorophenoxy) methyl)-1, 6-diphenyl-4-1H-pyrano [2, 3-c] pyrazol-4-one **(11)**: A solution of **10** (4.6 g, 10 mmol) in ethanol (40 mL) in the presence of piperidine (5 drops) was boiled for 6 h. The reaction mixture was concentrated and the colourless crystals after cooling, were filtered off, washed with a few drops of ethanol and recrystallised to yield **11** as yellow needles, m.p. 222–224 °C; (2.5 g, 53% yield). IR (KBr): ν_{max} 1685 (CO), 1523 (C=N) cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.91–3.05 (m, 2H, pyran CH_2), 5.30 (s, 2H, CH_2 phenoxy), 5.60 (dd, 1H, pyran H-2), 7.10–7.80 (m, 13H, ArH) ppm. Anal. Calcd for $C_{25}H_{18}Cl_2N_2O_3$ (465.34): C, 64.53; H, 3.90; N, 6.02. Found: C, 64.50; H, 3.80; N, 6.20%.

3-((2, 4-Dichlorophenoxy)methyl)-6, 6-dimethyl-1-phenyl-5, 6-dihydro-1H-pyrano [2, 3-c] pyrazol-4-one **(12)**: A mixture of **9b** (3.76 g, 10 mmol), acetone (0.6 g, 10 mmol) and pyrrolidine (0.7 g, 10 mmol) in dry benzene (100 mL) was refluxed using a Dean–Stark apparatus. After the calculated amount of water is eliminated, the reaction mixture was concentrated and left to cool. The solid formed was washed with petroleum ether, dried and recrystallised to yield **12** as yellow needles, m.p. 189–191 °C (2.5 g, 60% yield). IR (KBr): ν_{max} 1670 (CO), 1600 (C=N) cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.50 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 3.80 (s, 2H, CH_2), 5.10 (s, 2H, CH_2 phenoxy), 7.00–7.91 (m, 8H, ArH) ppm. MS: *m/z* (%) = 417 (20%) [M^+]. Anal. Calcd for $C_{21}H_{18}Cl_2N_2O_3$ (417.30): C, 60.45; H, 4.35; N, 6.71. Found: C, 60.50; H, 4.40; N, 6.50%.

Preparation of compounds **(13a-c);** *general procedure*

A mixture of **2a** and/or **2b** (20 mmol), benzaldehyde and/or anisalehyde (10 mmol), and triethylamine (1 mL) in ethanol (30 mL) was stirred for 2 h at 50 °C. The solution was evaporated to one-third volume; the separated precipitate was filtered off, washed with ethanol, dried, and recrystallised from the appropriate solvent.

3, 5-Bis((2, 4-dichlorophenoxy) methyl)-4-(4-methoxyphenyl)-4, 7-dihydro-1H-pyrano[2, 3-c; 6, 5-c'] dipyrazole **(13a)**: Yellow needles, m.p. 240–242 °C; (2.8 g, 45% yield). ^{1}H NMR (270 MHz, DMSO-d_6): δ 3.75 (s., 3H, OCH_3), 4.30 (s, 2H, CH_2 phenoxy), 4.80 (s, 1H, pyran H-4), 5.51 (s, 2H, CH_2 phenoxy), 7.10–7.84 (m, 10H, ArH), 10.11 (s, 1H, NH), 10.12 (s, 1H, NH) ppm. MS: *m/z* (%) = 617 (7%) [M^+–1]. Anal. Calcd for $C_{28}H_{20}Cl_4N_4O_4$ (618.31): C, 54.39; H, 3.26; N, 9.06. Found: C, 54.40; H, 340; N, 9.20%.

3, 5-Bis((2, 4-dichlorophenoxy) methyl)-4-phenyl-4, 7-dihydro-1H-pyrano[2, 3-c; 6, 5-c'] dipyrazole **(13b)**: Yellow needless, m.p. 198–200 °C (2.6 g, 44% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.50 (s, 2H, CH_2 phenoxy), 4.72 (s, 2H, CH_2 phenoxy), 4.90 (s, 1H, pyran H-4), 7.03–7.75 (m, 11H, ArH), 10.31 (s, 1H, NH), 10.43 (s, 1H, NH) ppm. ^{13}C NMR (400 MHz, DMSO-d_6): 61.27, 100.22, 115.65, 120.88, 123.15, 125.5, 127.26, 127.67, 128, 08, 128.36, 128.80, 129.79, 134.18, 144.16, 152.36, 161.17. MS: *m/z* (%) = 587 (6%) [M^+–1]. Anal. Calcd for $C_{27}H_{18}Cl_4N_4O_3$ (588.28): C, 55.13; H, 3.08; N, 9.52. Found: C, 55.20; H, 3.20; N, 9.60%.

3, 5-Bis((2, 4-dichlorophenoxy)methyl)-1, 4, 7-triphenyl-4, 7-dihydro-1H-pyrano [2, 3-c; 6, 5-c']dipyrazole **(13c)**: Yellow needles, m.p. 180–182 °C; (2.9 g, 39% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.10 (s, 2H, CH_2 phenoxy), 5.22 (s, 2H, CH_2 phenoxy), 5.30 (s, 1H, pyran H-4), 7.13–7.63 (m, 21H, ArH) ppm. ^{13}C NMR (400 MHz, DMSO-d_6): 65.71, 103.43, 115.01, 120.07, 122.54, 124.27, 124.70, 125.18, 127.58, 128.11, 128.78, 128.84, 129.49, 140.72, 144.68, 145.44, 153.20, 158.14. MS: *m/z* (%) = 759 (100%) [M^+ + H_2O]. Anal. Calcd for $C_{39}H_{26}Cl_4N_4O_3 \cdot H_2O$ (758.48): C, 61.76; H, 3.72; N, 7.39. Found: C, 61.80; H, 3.60; N, 7.50%.

Preparation of compounds **(14a**, **b);** *general procedure*

A solution of **2a** (2.85 g, 10 mmol) and the β-ketoester (10 mmol) in ethanol (30 mL) in the presence of piperidine (three drops) was refluxed for 4–6 h. The reaction mixture was concentrated to half of its volume and cooled. The solid product was precipitate, filtered off and recrystallised from methanol to give **14a** and/or **14b**, respectively.

3, 4-Bis((2, 4-dichlorophenoxy)methyl)-1H-pyrano[2, 3-c]-pyrazol-6-one **(14a)**: Pale yellow needles, m.p. 230–232 °C; (2.7 g, 60% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.87 (s, 2H, CH_2 phenoxy), 5.00 (s, 2H, CH_2 phenoxy), 5.80 (s, 1H, coumarin H-5) 7.02–7.61 (m, 6H, ArH), 10.30 (s, 1H, NH) ppm. ^{13}C NMR (400 MHz, DMSO-d_6): 60.41, 111.58, 115.72, 118.06, 122.77, 123.53, 125.43, 127.40, 128.41, 128.52, 129.72, 130.04, 140.36, 151.41, 152.56, 170.55. MS: *m/z* (%) = 486 (6%) [M^+]. Anal. Calcd for $C_{20}H_{12}Cl_4N_2O_4$ (486.13): C, 49.41; H, 2.49; N, 5.76. Found: C, 49.40; H, 2.60; N, 5.90%.

3-((2, 4-Dichlorophenoxy) methyl)-4-methyl-1H-pyrano [2, 3-c] pyrazol-6-one **(14b)**: Pale yellow needles, m.p. 142–144 °C; (2 g, 65% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82 (s, 1H, CH_3), 5.11 (s, 2H, CH_2 phenoxy), 5.98 (q, 1H, coumarin H-5) 7.00–7.60

(m, 3H, ArH), 10.30 (s, 1H, NH) ppm. Anal. Calcd for $C_{14}H_{10}Cl_2N_2O_3$ (325.15): C, 51.72; H, 3.10; N, 8.62. Found: C, 51.70; H, 3.20; N, 8.50%.

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