



SYNTHESIS OF BIOACTIVE HETEROCYCLES FROM 6-AMINO-4-(2-CHLORO-5-NITROPHENYL)-3-METHYL-1,4-DIHYDROPYRANO[2,3-*c*]PYRAZOLE-5-CARBONITRILE

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Enaminonitrile derivative, 6-amino-4-(2-chloro-5-nitrophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**1**) was synthesized. This compound was utilized as a building block for the synthesis of new 3-methylpyrazolopyran moiety incorporated with different heterocycles involving pyrimidinone, oxazinone, and iminopyrimidine, in addition to novel derivatives including diacetyl derivative (**5**), benzoyl derivative (**6**), carbamodithioic acid (**10**) and urea derivative (**13**). Spectral techniques, FT-IR, ¹H-NMR and mass spectroscopy and elemental analysis were used to characterize the synthesized compounds. Screening and evaluation of these products as antimicrobial agents showed that the derivatives **5**, **6**, **10**, and **13** possess a potent activity.

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Introduction

It has been reported that pyran derivatives possess hypotensive effect,¹ anticancer activity,² antifungal effect,^{3,4} plant growth regulation activity.⁵ Pyranopyrazoles are important compounds for the preparation of many biological active heterocyclic compounds⁶ and they proved to have useful properties as therapeutics in clinical application.⁷⁻⁹ A literature survey revealed that pyrazole derivatives have received much attention during the recent years on account of their utilization as antioxidant,¹⁰ antihypertensive,¹¹ antifungal^{12,13} and vasodilator.¹⁴ As well as, pyrimidinone derivatives have extensive applications as structural units of various biologically important molecules and as useful intermediates in medicinal chemistry¹⁵ and pyranopyrimidinones compounds showed considerable pharmaceutical and biological activities, including anticancer, antitumor, antimalarial, antibacterial, antihypertensive, anti-inflammatory, hepatoprotective, cardiogenic, vasodilator, bronchodilator, antifolate, and antiallergic activities.¹⁶⁻²⁸ They are also used in the preparation of dyes and pigments flavoring agents,^{29,30} and in luminescence chemistry.³¹ Over the past decades, significant efforts have been devoted to develop the synthesis of pyrimidinethione derivatives,^{32,33} as they are considered versatile synthons for the construction of many heterocycles of synthetic and biological importance.³⁴⁻³⁷ Thus, in view of the above facts and in continuation of our efforts to construct heterocyclic compounds from pyran derivatives, and to study their biological potency,³⁸⁻⁴⁵ it was of interest to synthesize a ring system combine both the pyrazole and the pyran moieties which might have good biological activity.

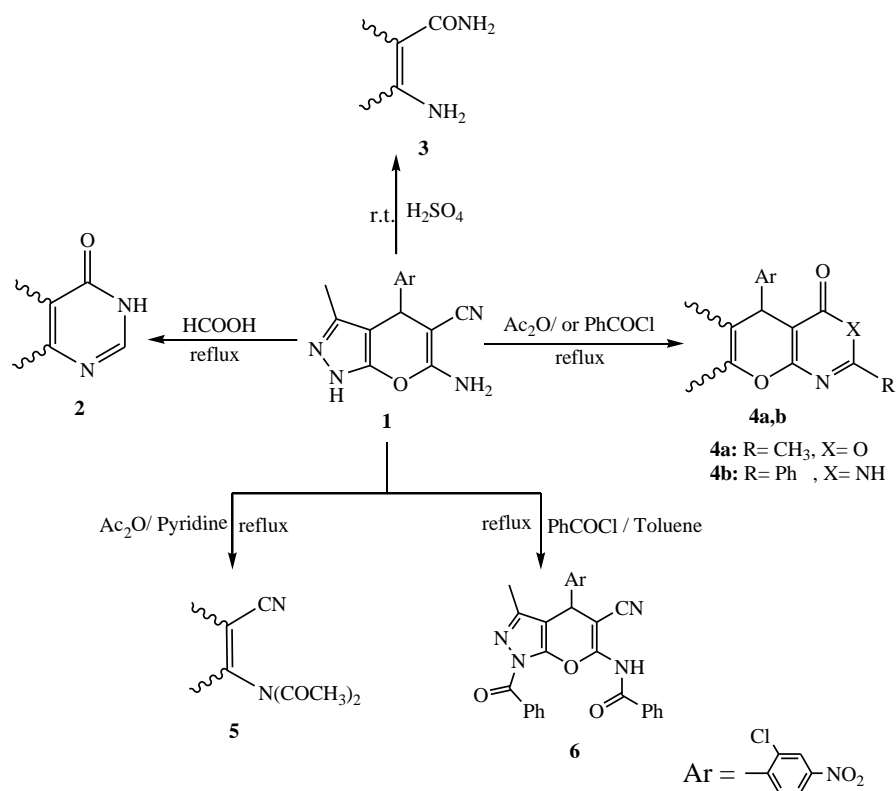
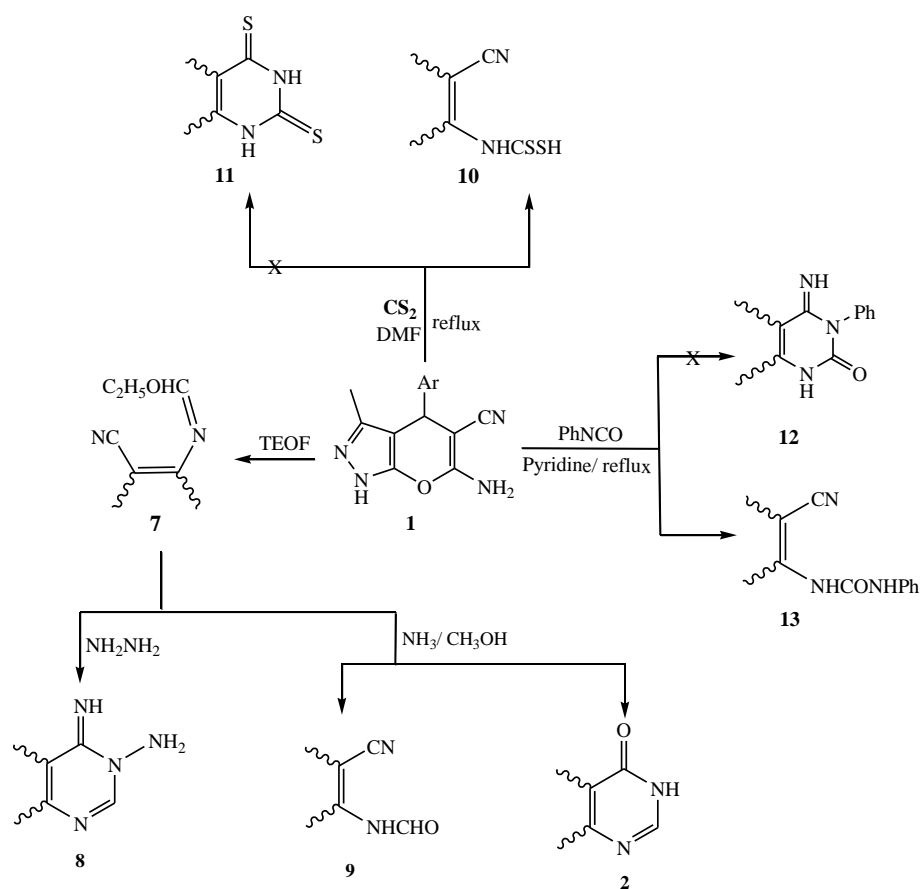
Results and Discussion

Syntheses

The previously reported⁴⁶ pyranopyrazole derivative (**1**) was allowed to react with different reagents aiming to synthesize antimicrobial heterocycles. Reaction of **1** with formic acid afforded the pyrimidinone derivative **2** whose structure was confirmed from IR spectral data which revealed the absence of absorption bands of C≡N and NH₂ groups and the appearance of bands characteristic to carbonyl and NH groups at ν 1682 cm⁻¹ and 3182 cm⁻¹, respectively. The ¹H-NMR spectrum showed a singlet at δ 11.08 ppm, disappeared by D₂O due to NH group proton. Acid hydrolysis of the cyano functionality was carried out by addition of concentrated sulphuric acid onto pyranopyrazole derivative **1** at room temperature to give the amide derivative **3**. The structure of the amide **3** was elucidated by the FTIR spectra which showed no absorption band of C≡N and appearance of a new band due to C=O group at ν 1685 cm⁻¹.

In our previously reported work for the synthesis of oxazinone derivatives,⁴⁶ the pyranopyrazole derivative **1** was allowed to react with acetic anhydride and/or benzoyl chloride under solvent-free conditions and afforded the pyrazolopyranooxazinones **4a**, **b**. On the contrary, herein, the reaction of **1** with acetic anhydride in pyridine gave the diacetyl derivative **5** and benzylation with benzoyl chloride in dry toluene as a solvent afforded the benzoyl derivative **6**. The IR spectra of both products **5** and **6** revealed the presence of cyano group absorption that proved no cyclization has occurred (Scheme 1).

To make use of nucleophilic character of the amino group, it was subjected to react with various electrophiles. Thus, when enaminonitrile **1** was treated with triethyl orthoformate, it gave the imidoformate derivative **7**. The latter product was utilized as a precursor for the synthesis of pyrazolopyranopyrimidine **8** by reaction with hydrazine hydrate in ethanol. The structure of **7** was confirmed from its IR spectrum that did not show the absorption frequency of NH₂ group but showed the C=N group band at 1632 cm⁻¹.

**Scheme 1.** Reactions of pyranopyrazole derivative.**Scheme 2.** Further reactions of pyranopyrazole derivatives

Further, the $^1\text{H-NMR}$ spectrum showed a singlet at δ 12.36 ppm which disappeared in D_2O and is due to NH group, a quartet peak owing to CH_2 group at δ 4.34-4.28 ppm and a triplet peak at δ 1.31-1.28 ppm due to CH_3 protons.

The structure of **8** has been elucidated on the basis of IR spectrum which showed a coupling band at 3188, 3119 cm^{-1} due to NH_2 group and two peaks for NH pyrazole and NH imino at 3349 and 3309 cm^{-1} , respectively. Its $^1\text{H-NMR}$ spectrum showed a singlet at δ 12.57 ppm NH of pyrazole group and 10.25 ppm for C=NH . However, when the imidoformate derivative **7** was subjected to react with ammonium hydroxide in methanol, hydrolysis of the imidoformate functionality to the formamide derivative **9** occurred instead of the formation of the pyrimidinone derivative **2**.

Further, treatment of the enamionitrile **1** with carbon disulfide afforded carbamodithioic acid **10** instead of pyrimidenedithione derivative **11**. The IR spectrum of **10** revealed the absorption band attributable to $\text{C}\equiv\text{N}$ group at 2215 cm^{-1} and a sharp band at 1390 cm^{-1} due to C=S group. The reaction of the compound **1** with phenylisocyanate in pyridine provided the urea derivative **13** instead of the pyrimidinone derivative **12**. The structure of **13** was confirmed from its elemental and spectral analysis (Scheme 2).

Antimicrobial Study

The antibacterial activity of the synthesized compounds **2**, **3**, **7**, **8**, **10** and **13** was tested against a panel of two gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). The antifungal activities of the compounds were tested against two fungi (*Candida albicans* and *Aspergillus flavus*).

Each compound was dissolved in DMSO and a solution of concentration 1 mg mL^{-1} were prepared. Separately paper discs (5cm) were cut and sterilized in an autoclave. The paper discs, soaked in the solution of the compound, were placed aseptically in the petri dishes containing nutrient agar media (agar 20g + beef extract 3g + peptone 5g) seeded with *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans* and *Aspergillus flavus*. The petri dishes were incubated at 36 $^{\circ}\text{C}$ and the inhibition zones were recorded after 24 h of incubation. Each treatment was replicated three times. The antibacterial activity of a common standard antibiotic ampicillin and antifungal colitrimazole was also recorded using the same procedure as above at the same concentration and solvents.

The % activity index for the complex was calculated by the formula as shown below:

$$\text{Activity index (\%)} = 100 \frac{\text{zone of inhibition by test compound}}{\text{zone of inhibition by standard}}$$

The antimicrobial activity of the synthesized heterocycles was shown in Table 1.

Minimum inhibitory concentration (MIC) measurements

The MIC was determined using the disc diffusion technique by preparing discs containing 1.9-1000 $\mu\text{g/mL}$ of each compound against gram positive *Staphylococcus aureus* and *Bacillus subtilis* and gram negative *Escherichia coli* and *Pseudomonas aeruginosa*. The antifungal activities of the compounds were tested against two fold fungi *Candida albicans* and *Aspergillus flavus* and applying the protocol. The two fold dilutions of the solution were prepared. The microorganism suspensions at 10 CFU/ mL (colony forming unit/mL) concentration were inoculated to the corresponding wells. The plates were incubated at 36 $^{\circ}\text{C}$ for 24 h. for the bacteria. The standard antibiotic ampicillin and Antifungal Colitrimazole was also recorded using the same procedure as above at the same concentration and solvents. At the end of the incubation period, the minimum inhibitory concentration (MIC) values were recorded as the lowest concentration of the substance that had no visible turbidity. Control experiments with DMSO and uninoculated media were run parallel to the test compounds under the same condition. The results of MIC measurements of the synthesized heterocycles compounds are shown in Table 2.

Experimental

All melting points were determined on an electrothermal apparatus and are uncorrected. The FT-IR were recorded in potassium bromide disks on Pye Unicam SP3-300 and Shimadzu FTIR 8101PC Infrared spectrophotometers. The $^1\text{H-NMR}$ was recorded on a Varian Mercury VX-300 NMR spectrometer. $^1\text{H-NMR}$ spectra were run at 300 MHz and on a Varian Gemini 200 MHz, Bruker AC 200 MHz using TMS as internal standard in deuterated chloroform (CDCl_3) or deuterated dimethyl sulfoxide ($\text{DMSO}-d_6$). Chemical shifts are quoted in δ and were related to that of the solvents. The mass spectra were recorded on a Shimadzu GC-MS QP1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Micro analytical Center of Cairo University. All the reactions and the purity of the new compounds were followed and checked by TLC.

Synthesis

4-(2-Chloro-5-nitrophenyl)-3-methyl-4,6-dihydropyrazolo-[4',3':5,6]pyrano[2,3-d]pyrimidin-5(1H)-one (**2**)

A mixture of **1** (5 mmol, 1.66 g) and formic acid (20 mL) was refluxed for 2 h, the reaction mixture was poured after cooling into water and crushed ice, the solid formed was filtered off, washed with cold water and crystallized from ethanol to give compound **2** as a pale yellow solid (72 %). m.p. 229-230 $^{\circ}\text{C}$. IR (KBr): 3403 (NH pyraz.), 3182 (NH pyrim.), 1682 (CO) cm^{-1} . MS m/z (%) 359 (M^+ , 7.35), 360 (3.42), 230 (74.53), 179 (2.15), 43 (100). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ = 11.4 (s, 1H, NH), 11.08 (s, 1H, NH), 8.49 (s, 1H, CH, N = C2-H), 8.07-7.70 (m, 3H, aromatic), 4.64 (s, 1H, benzylic), 2.12 (s, 3H, CH_3). Anal. Calcd. for $\text{C}_{15}\text{H}_{10}\text{N}_5\text{O}_4\text{Cl}$ (359.73): C, 20.08; H, 2.80; Cl, 9.85; N, 19.47. Found: C, 20.06; H, 2.82; Cl, 9.83; N, 19.48.

Table 1. Antimicrobial study of the synthesized heterocycles compounds

Compound	<i>E. coli</i> , mg mL ⁻¹		<i>P. aeruginosa</i> , mg mL ⁻¹		<i>S. aureus</i> mg mL ⁻¹		<i>B. subtilis</i> mg mL ⁻¹		<i>C. albicans</i> mg mL ⁻¹		<i>A. flavus</i> mg mL ⁻¹	
	DIZ, mm	% AI	DIZ, mm	% AI	DIZ, mm	% AI	DIZ, mm	% AI	DIZ, mm	% AI	DIZ, mm	% AI
2	9	36.0	16	69.6	14	60.9	16	69.6	8	30.8	12	48.0
3	13	52.0	20	86.9	15	65.2	18	78.3	21	80.8	20	80.0
7	NA	----	2	8.7	2	8.7	NA	----	NA	----	NA	----
8	NA	----	5	21.7	4	17.4	6	26.1	NA	----	7	28.0
10	5	20.0	9	39.1	9	39.1	10	43.5	5	19.2	9	36.0
13	7	28.0	11	47.8	10	43.5	13	56.5	10	38.5	18	72.0
Ampicillin	25	100	23	100	23	100	23	100	NA	----	NA	----
Colitrim-azole	NA	----	NA	----	NA	----	NA	----	26	100	25	100

DIZ = Diameter of inhibition zone; % AI = % Activity index; NA = No activity

Table 2. Antimicrobial and antimycotic activities in terms of MIC ($\mu\text{g mL}^{-1}$).

Compound	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>B. subtilis</i>	<i>C. Albicans</i>	<i>A. flavus</i>
2	250	187.5	93.7	187.5	93.7	46.9
3	187.5	125	62.5	187.5	23.4	7.8
7	NA	750	500	NA	NA	NA
8	NA	500	375	750	NA	250
10	750	375	250	375	187.5	62.5
13	375	250	187.5	250	46.9	23.4
Ampicillin	125	187.5	93.7	187.5	----	----
Colitrimazole	----	----	----	----	7.8	5.8

6-Amino-4-(2-chloro-5-nitrophenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carboxamide (3)

Compound **1** (5 mmol, 1.66 g) was added drop wise with stirring to concentrated cold sulphuric acid (6 mL) at 20 °C, the temperature did not exceed 40 °C during the addition, then the solution was stirred for further 1 h at room temperature and poured onto ice cold water (10 mL). The reaction mixture was left overnight in the refrigerator. The yellow precipitate was filtered off and crystallized from water to give compound **3** as a pale yellow solid (68 %). m.p. 175-176 °C. FTIR (KBr): 3588 (NH pyraz.), 3567-3370 (NH₂), 3191-3108 (amide NH₂), 1685 (CO) cm⁻¹. MS *m/z* (%): 350(M⁺; 1.36), 351(4.93), 307 (67.39), 230(70.44), 151 (43.39), 43(100). ¹H-NMR (DMSO-*d*₆) δ = 11 (s, 1H, NH, pyraz., exchanged with D₂O), 7.38- 6.67 (s, 4H, C2-NH₂; CONH₂, exchanged with D₂O), 8.63-7.60 (m, 3H, aromatic), 4.68 (s, 1H, benzylic), 2.1 (s, 3H, CH₃). Anal. Calcd. for C₁₄H₁₁N₄O₅Cl (350.72): C, 47.95; H, 3.16; Cl, 10.11; N, 15.98. Found: C, 47.93; H, 3.15; Cl, 10.11; N, 15.99.

N-Acetyl-N-[4-(2-chloro-5-nitrophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-yl]acetamide (5)

A solution of **1** (5 mmol, 1.66 g) in acetic anhydride-pyridine mixture (30 mL, 2:1 v/v) was heated on a water bath for 8 h, then cooled and poured into ice/ water mixture. The precipitate thus formed was filtered off, washed several times with water, dried and crystallized from dioxane to give compound **5**, as a deep brown solid (50 %). m.p. > 300 °C. FTIR (KBr): 3355(NH pyrazole), 1787, 1739 (C=O), 2223(C \equiv N) cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ = 11.28 (s, 1H,

NH, pyrazole, exchanged with D₂O), 8.42-7.70 (m, 3H, aromatic), 4.62 (s, 1H, benzylic), 2.12 (s, 6H, 2CH₃), 2.55 (s, 3H, CH₃). MS *m/z* (%): 415 (M⁺; 100), 417(32), 416 (19.5). Anal. Calcd. for C₁₈H₁₄N₅O₅Cl (415.79): C, 52; H, 3.39; Cl, 8.53; N, 16.84. Found: C, 52.01; H, 3.38; Cl, 8.52; N, 16.85.

N-[4(2-Chloro-5-nitrophenyl)-5-cyano-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazol-6-yl]benzamide (6)

A mixture of **1** (5 mmol, 1.66 g) and benzoyl chloride (5 mmol) in toluene was refluxed for 24 h. The excess of solvent was removed under vacuum, the remaining solid was crystallized from ethanol-dioxane (1:1) to give compound **6** as a brown solid (53 %). m.p. 261-262 °C. FTIR (KBr): 3452 (NH pyrazole), 3168 (NH-amide), 1708 (C=O, cyclic amide), 2193 (C \equiv N), 1641 (C=O, amide) cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ = 8.35 (s, 1H, NH, amide), 8.19-7.40 (m, 13H, aromatic), 5.41 (s, 1H, benzylic), 1.79 (s, 3H, CH₃). MS *m/z* (%): 539 (M⁺; 3.40), 541 (2.38), 426 (15.76), 220 (28.65), 41(100). Anal. Calcd. for C₂₈H₁₈N₅O₅Cl (539.93): C, 62.29; H, 3.36; Cl, 6.57; N, 12.97. Found: C, 62.27; H, 3.35; Cl, 6.56; N, 12.98.

Ethyl-4-(2-chloro-5-nitrophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-ylimidoformate (7)

A mixture of **1** (5 mmol, 1.66 g) and triethyl orthoformate (20 mL) was refluxed for 24 h. After completion of the reaction, the excess of triethyl orthoformate was removed under vacuum. The remaining solid was washed with n-hexane several times and crystallized from benzene to give

compound **7** as a pale brown solid (60 %). m.p. 233-234 °C. FTIR (KBr.): 3180 (NH pyrrazole), 1632 (C=N), 2210 (C≡N) cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ = 12.36 (s, 1H, NH, pyrazole, exchanged with D₂O), 8.59 (s, 1H, N=CH), 8.17–7.77 (m, 3H, aromatic), 5.47 (s, 1H, benzylic), 4.34–4.28 (q, 2H, CH₂), 1.77 (s, 3H, CH₃, pyrazole), 1.31–1.28 (t, 3H, CH₃). MS *m/z* (%): 386.87(M⁺; 11.08), 389(5.67), 283(25.01), 259(34.62), 202(32.17), 146 (82.33), 82 (100). Anal. Calcd. for C₁₇H₁₄N₅O₄Cl (387.78): C, 52.66; H, 3.64; Cl, 9.14; N, 18.06. Found: C, 52.64; H, 3.62; Cl, 9.13; N, 18.08.

4-(2-chloro-5-nitrophenyl)-5-imino-3-methyl-1,4-dihydropyrazolo-[4',3':5,6]pyrano[2,3-d]pyrimidin-6- (5H)-amine (8)

To a well stirred cold solution of compound **7** (20 mmol, 7.76 g) in ethanol (20 mL), hydrazine monohydrate (99 %) (3 mL) was added drop wise and then the mixture was stirred at room temperature for 6 h and left overnight. The solid that precipitated was filtered off and and crystallized from ethanol to give compound **8** as a pale yellow solid (66 %). m.p. > 300 °C. FTIR (KBr.): 3349 (NH pyrrazole), 3309 (NH, imino), 3188, 3119 (NH₂), 1638 (C=N) cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ = 12.57 (s, 1H, NH, pyrazole), 10.25 (s, 1H, C=NH), 8.44 (s, 1H, CH=N), 8.18–7.67 (m, 3H, aromatic), 5.89 (s, 1H, benzylic), 4.40 (s, 2H, NH₂), 1.93 (s, 3H, CH₃). MS *m/z* (%): 373 (M⁺; 2.43), 290 (13.60), 221 (21.71), 161 (65.56), 60 (100). Anal. Calcd. for C₁₅H₁₂N₇O₃Cl (373.76): C, 48.20; H, 3.24; Cl, 9.48; N, 26.23. Found: C, 48.21; H, 3.23; Cl, 9.47; N, 26.24.

4-(2-Chloro-5-nitrophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-yl formamide (9)

Compound **7** (2 mmol, 0.78 g) was added to a mixture of methanol (15 mL) and 25% aqueous ammonia solution (15 mL). The reaction mixture was stirred for 24 h, cooled, and the precipitated solid was filtered off and crystallized from toluene to give compound **9** as a pale brown solid (51 %). m.p. > 300 °C. FTIR (KBr.): 3271(NH pyrrazole), 2205 (C≡N), 1669 (CO) cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ = 12.57 (s, 1H, NH, pyrazole), 8.21 (s, 1H, CHO), 8.32–7.68 (m, 3H, aromatic), 7.2 (s, 1H, NH), 4.74 (s, 1H, benzylic), 1.9 (s, 3H, CH₃). Anal. Calcd. for C₁₅H₁₀N₅O₄Cl (359.73): C, 50.08; H, 2.80; Cl, 9.48; N, 26.23. Found: C, 48.21; H, 3.23; Cl, 9.47; N, 26.24.

4-(2-Chloro-5-nitrophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-yl carbamodithioic acid (10)

To a solution of **1** (10 mmol, 3.31 g) in DMF (20 mL), carbon disulfide (15 mmol) and 10 mL of sodium methoxide (prepared from 0.59 gm of sodium metal and 30 ml methanol) were added. The mixture was refluxed for 20 h and then poured into ice cold water. A solution of sodium hydroxide (20 mL, 1M) was added to it and left overnight. The solution was filtered and acidified with dilute acetic acid to give yellow precipitate, which was collected, washed with dilute acetic acid, dried and crystallized from ethanol to give compound **11** as a deep yellow solid (52 %). m.p. > 300 °C. FTIR (KBr): 3261 (NH pyrrazole), 3151(NH), 2966 (SH), 2215 (C≡N), 1390 (C=S) cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ = 12.02 (s, 1H, NH, pyrazole), 7.70–7.14 (m, 3H,

aromatic), 5.52 (s, 1H, benzylic), 10.89 (s, 1H, NH), 1.2(s, 1H, SH), 1.9 (s, 3H, CH₃). MS *m/z* (%):406.9 (M⁺; 6.07), 409 (4.64), 358 (32.16), 281 (25.37), 64 (100). Anal. Calcd. for C₁₅H₁₀N₅O₃S₂Cl (407.85): C, 44.17; H, 2.47; Cl, 8.69; N, 17.17. Found: C, 44.16; H, 2.46; Cl, 8.68; N, 17.18.

N-[4-(2-Chloro-5-nitrophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-yl]-N'-phenyl- urea (13)

A mixture of **1** (10 mmol, 3.31 g) and phenylisocyanate (10 mmol) in pyridine (20 mL) was refluxed for 12 h. The reaction mixture was cooled and poured onto ice/ water mixture and neutralized with diluted HCl. The solid product so formed was collected by filtration and crystallized from methanol to give compound **13** as a deep yellow solid (56 %). m.p. > 300 °C. FTIR (KBr): 3371 (NH pyrrazole), 3213, 3101 (2NH, amide), 1745 (C=O), 2210 (C≡N) cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ = 11.5 (s, 1H, NH, pyrazole), 8.58–7.11 (m, 8H, aromatic), 4.7(s, 1H, benzylic), 8.9 (s, 1H, NH), 6.7 (s, 1H, NH), 1.9 (s, 3H, CH₃). MS *m/z* (%):450 (M⁺; 3.47), 451.85 (4.90), 244 (22.11), 219 (41.50), 198 (79.99). Anal. Calcd. for C₂₁H₁₅N₆O₄Cl (450.84): C, 55.95; H, 3.35; Cl, 7.86; N, 18.64. Found: C, 55.94; H, 3.33; Cl, 7.87; N, 18.65.

References

- Goel, A., Singh, F. V., *Tetrahedron Lett.*, **2005**, 46, 5585-5587. <https://doi.org/10.1016/j.tetlet.2005.06.034>
- EL-Far, M., EL megeed, F. V. G. A., Eskander, E. F., Rady, H. M., Tantawy, M. A., *Eur. J. Med. Chem.*, **2009**, 44 (10), 3936-3946. <https://doi.org/10.1016/j.ejmech.2009.04.020>
- Pasternak, P. V., Averkiev, Antipin, B. B. M. Y., Peregodov, A. S., Chkanikov, N. D. *J. Fluorine Chem.*, **2004**, 125, 1853-1868. <https://doi.org/10.1016/j.jfluchem.2004.06.008>
- Ballini, R., Sartori, G., Sartorio, R., *Tetrahedron Lett.*, **2004**, 45, 2297-2299. <https://doi.org/10.1016/j.tetlet.2004.01.115>
- Abdel hamid, A. O., Afifi, M. A. M., *J. Adv. Res.*, **2010**, 1, 137-144. <https://doi.org/10.1016/j.jare.2010.03.005>
- Al-Amiery, A. A., Al-Bayati, R. I., Saed, F. M., Ali, W. B., Kadhum, A. A. H., Mohamad, A. B., *Molecules*, **2012**, 17, 10377-10389. [10.3390/molecules170910377](https://doi.org/10.3390/molecules170910377)
- El-Gazzar, A. B. A., El-Enany, M. M., Mahmoud, M. N., *Bioorg. Med. Chem.*, **2008**, 16, 3261-3273. <https://doi.org/10.1016/j.bmc.2007.12.012>
- Fayed, A. A., Hosni, H. M., Flefel, E. M., Amr, A. E. E., *World J. Chem.*, **2009**, 4, 58-65.
- Sondhi, S. M., Singh, N., Johar, M., Kumar, A., *Bioorg. Med. Chem.*, **2005**, 13, 6158-6166. <https://doi.org/10.1016/j.bmc.2005.06.063>
- Abu-Hashem, A. A., El-Shehry, M. F., Badria, F. A., *Acta Pharm.*, **2010**, 60, 311-323. <https://doi.org/10.2478/v10007-010-0027-6>
- Svetlik, J., Veizerova, L., Liptaj, T., Kubista, J., *ARKIVOC*, **2009**, 2009, 79-86. <http://dx.doi.org/10.3998/ark.5550190.0010.a09>
- Fathalla, O. A., Zeid, I. F., Haiba, M. E., Soliman, A. M.; Abd-Elmoez, S. I.; Serwy, W. S. *World J. Chem.*, **2009**, 4, 127-132.
- El-Assiery, S. A., Sayed, G. H., Fouda, A., *Acta Pharm.*, **2004**, 54, 143-150.

- ¹⁴Li, M., Wang, S. W., Wen, L. R., Qi, W. Y., Yang, H. Z., *J. Chin. Chem. Soc.*, **2005**, 52, 1021-1028. [10.1002/jccs.200500143](https://doi.org/10.1002/jccs.200500143)
- ¹⁵Wannberg, J., Dallinger, D., Kappe, C.O., Larhed, M. J., *Comb. Chem.*, **2005**, 7, 574-583. <http://dx.doi.org/10.1021/cc049816c>
- ¹⁶Alqasoumi, S. I., Al-Taweel, A. M., Alafeefy, A. M., Noaman, E., Ghorab, M. M., *Eur. J. Med. Chem.*, **2010**, 45, 738-744. <https://doi.org/10.1016/j.ejmech.2009.11.021>
- ¹⁷Broom, A. D., Shim, J. L., Anderson, G. L., *J. Org. Chem.*, **1976**, 41, 1095-1099. [10.1021/jo000869a003](https://doi.org/10.1021/jo000869a003)
- ¹⁸Joshi, A. A., Viswanathan, C. L., *Anti-Infect. Agents Med. Chem.*, **2006**, 5, 105-122. <https://doi.org/10.2174/187152106774755626>
- ¹⁹Ghorab, M. M., Hassan, A. Y., *Phosphorus, Sulfur Silicon Relat. Elem.*, **1998**, 141, 251-261. <https://doi.org/10.1080/10426509808033737>
- ²⁰Sharma, P., Rane, N., Gurram, V. K., *Bioorg. Med. Chem. Lett.*, **2004**, 14, 4185-4190. <https://doi.org/10.1016/j.bmcl.2004.06.014>
- ²¹El-Gazzar, A. B. A., Hafez, H. N., Nawwar, G. A. M., *Eur. J. Med. Chem.*, **2009**, 44, 1427-1436. <https://doi.org/10.1016/j.ejmech.2008.09.030>
- ²²De la Cruz, J. P., Moreno, A., Mérida, F., García-Campos, J., de la Cuesta, F. S., *Pharmacol. Toxicol.*, **1994**, 75, 250-254. [10.1111/j.1600-0773.1994.tb00356.x](https://doi.org/10.1111/j.1600-0773.1994.tb00356.x)
- ²³Gupta, R., Jain, A., Joshi, R., Jain, M., *Bull. Korean Chem. Soc.*, **2011**, 32, 899-904. [10.5012/bkcs.2011.32.3.899](https://doi.org/10.5012/bkcs.2011.32.3.899)
- ²⁴Hanna, M. M., *Eur. J. Med. Chem.*, **2012**, 55, 12-22. <https://doi.org/10.1016/j.ejmech.2012.06.048>
- ²⁵Shinde, S. V., Jadhav, W. N., Karade, N. N., *Orient. J. Chem.*, **2010**, 26, 307-317.
- ²⁶Lichtner, R. B., Hutchinson, G., Hellmann, K., *Eur. J. Cancer Clin. Oncol.*, **1989**, 25, 945-951. [https://doi.org/10.1016/0277-5379\(89\)90152-1](https://doi.org/10.1016/0277-5379(89)90152-1)
- ²⁷DeGraw, J. I., Christie, P. H., Clowell, W. T., Sirotinak, F. M., *J. Med. Chem.*, **1992**, 35, 320-324. [10.1021/jm00080a017](https://doi.org/10.1021/jm00080a017)
- ²⁸Thomas, H. D., Saravanan, K., Wang, L. Z., Lin, M. J., Northen, J. S., Barlow, H., Barton, M., Newell, D. R., Griffin, R. J., Golding, B. T., Curtin, N. J., *Mol. Cancer Therapy*, **2009**, 8, 1828-1837. [10.1158/1535-7163.MCT-08-1208](https://doi.org/10.1158/1535-7163.MCT-08-1208)
- ²⁹Petal, N. C., Mehta, A. G., *Asian J. Chem.*, **2001**, 13, 1385-1388.
- ³⁰Holla, B. S., Mahalinga, M., Karthikeyan, M. S., Akberali, P. M., Shetty, N. S., *Bioorg. Med. Chem.*, **2006**, 14, 2040-2047. <https://doi.org/10.1016/j.bmc.2005.10.053>
- ³¹Całus, S., Gondek, E., Danel, A., Jarosz, B., Pokładko, M., Kityk, A. V., *Mater. Lett.*, **2007**, 61, 3292-3295. <https://doi.org/10.1016/j.matlet.2006.11.055>
- ³²Yousif, N. M., Gad, F. A., Sayed, H. H., *Egypt. J. Chem.*, **1992**, 35, 101-110.
- ³³Yousif, N. M., Gad, F. A., Sayed, H. H., *Egypt. J. Pharm. Sci.*, **1996**, 37, 145-156.
- ³⁴Sayed, H. H., *Indian J. Chem.*, **1998**, 37B, 1054-1058.
- ³⁵Sayed, H. H., Fahmy, F. A., *Egypt. J. Chem.*, **2001**, 44, 365-372.
- ³⁶Rashad, A. E., Sayed, H. H., Shamroukh, A. H., Awad, H. M., *Phosphorus Sulfur*, **2005**, 180, 2767-2777. <https://doi.org/10.1080/104265090968118>
- ³⁷Abdel-Megeid, F. M. E., Hassan, N. A., Zahran, M. A., Rashad, A. E., *Sulfur Lett.*, **1998**, 21, 269-284.
- ³⁸El-Ziaty, A. K., Abdalha, A. A., Hamed, A. A., Shiba, S. A., Abdulalh, A. A., *Eur. J. Chem.*, **2012**, 3(1), 65-70. [10.5155/eurjchem.3.1.65-70.518](https://doi.org/10.5155/eurjchem.3.1.65-70.518)
- ³⁹El-Ziaty, A. K., Shiba, S. A., *Synth. Commun.*, **2007**, 27, 4043-4057. <https://doi.org/10.1080/00397910701575491>
- ⁴⁰Abou-Elmagd, W. S. I., EL-Ziaty, A. K., Abdalha, A. A., *Heterocycl. Commun.*, **2015**, 21(13), 179-185. <https://doi.org/10.1515/hc-2015-0008>
- ⁴¹Elziaty, A. K.; Mostafa, O. E. A.; El-Bordany, E. A.; Nabil, M.; Madkour, H.M.F. *Int. J. Sci. Eng. Res.* **2014**, 5, 727-735.
- ⁴²Ismail, M. F., Mahmoud, M. R., Shiba, S. A., El-Ziaty, A. K., Abu El-Azm, F. S. M., *Synth. Commun.*, **2014**, 44, 1094-1102. <https://doi.org/10.1080/00397911.2013.846381>
- ⁴³El-Ziaty, A. K., Hussein, A. M., Mahmoud, M. R., *World Appl. Sci. J.*, **2012**, 17(1), 101-108.
- ⁴⁴Morsy, J. M., Aly, A. F., Elshahawi, M. M., EL-Ziaty, A. K., *J. Heterocycl. Chem.*, **2016**, 53 (5), 1443-1448. [10.1002/jhet.2445](https://doi.org/10.1002/jhet.2445)
- ⁴⁵EL-Ziaty, A. K., El-Shahawi, M. M., *J. Chem.* **2017**. <https://doi.org/10.1155/2017/5610707>
- ⁴⁶EL-Ziaty, A. K., Abdel-Aziz, M. S., Bassioni, G., Hassan, A. M. A., Derbala, H. A., *J. Chem.*, **2016**. <http://dx.doi.org/10.1155/2016/5286462>

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