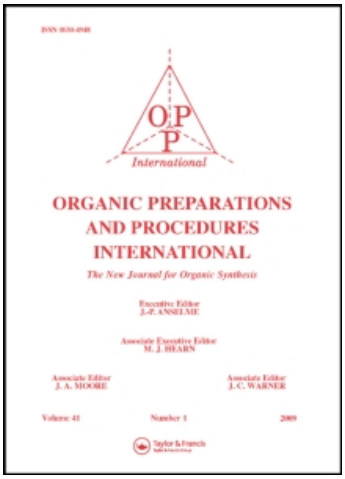

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5-CARBETHOXY- AND 5-ACETYLPYRAZOLES AS PRECURSORS FOR THE SYNTHESIS OF SOME NOVEL 1-*p*-CHLOROPHENYLPYRAZOLE-3-CARBONITRILES

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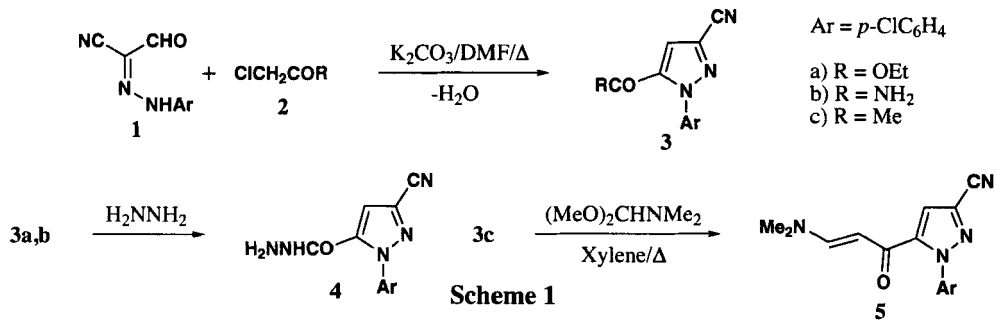
The pyrazole subunit has found widespread applications in therapeutically active compounds, including anticonvulsants,[1] analgesics,[2,3] anti-inflammatory drugs,[4-7] and human immunodeficiency virus (HIV) inhibitors.[8] Many other derivatives have been documented to be effective as antimicrobial[9-12] and antitumor[13-15] agents. Recently, aminopyrazoles were found to be potentially useful in the prevention of protein aggregation which is the first phase of Alzheimer or Creutzfeldt-Jakob diseases.[16,17] In addition, pyrazoles are important synthons for the preparation of biologically active derivatives.[18-20] Furthermore, the pyrazole subunit also plays an important role in material science as it is found in agrochemicals (insecticides) and dyes.[21-24] The synthesis of this important family of compounds has been reviewed.[25-27] The conventional approach to pyrazoles is based on the reaction of hydrazines with 1,3-difunctional compounds,[28] such as 1,3-diketones,[1,2,9-11] β-ketoesters,[4,9] β-cyanoketones,[20] and 1,3-dinitriles.[29,30] The reaction of hydrazones with 1,3-dicarbonyl compounds to give pyrazoles has been recently reported[31] as well as the cycloaddition of hydrazones to maleimides.[32,33] Although these methods are useful when the appropriate starting materials are available, there exist limitations that make access to certain classes of pyrazoles difficult or impossible using these methods. For instance, some particular derivatives of pyrazole are obtained through regiospecific reaction process involving the ring transformation of 5-acylpyrimidines into 4-acylpyrazoles under the action of hydrazines in acidic conditions.[26] Moreover, the ring contraction reactions of 5-acyluracils with hydrazines also open a convenient access to other derivatives of pyrazole-4-carboxylic acid, which are otherwise difficult to synthesize or even inaccessible.[26] As a continuation of our medicinal program,[34-36] derivatives of *N*-arylcyanopyrazole bearing various bioactive heterocycles became a topic of interest.[37] The present investigation describes the synthesis of these compounds from 5-substituted-pyrazole-3-carbonitriles **3**.

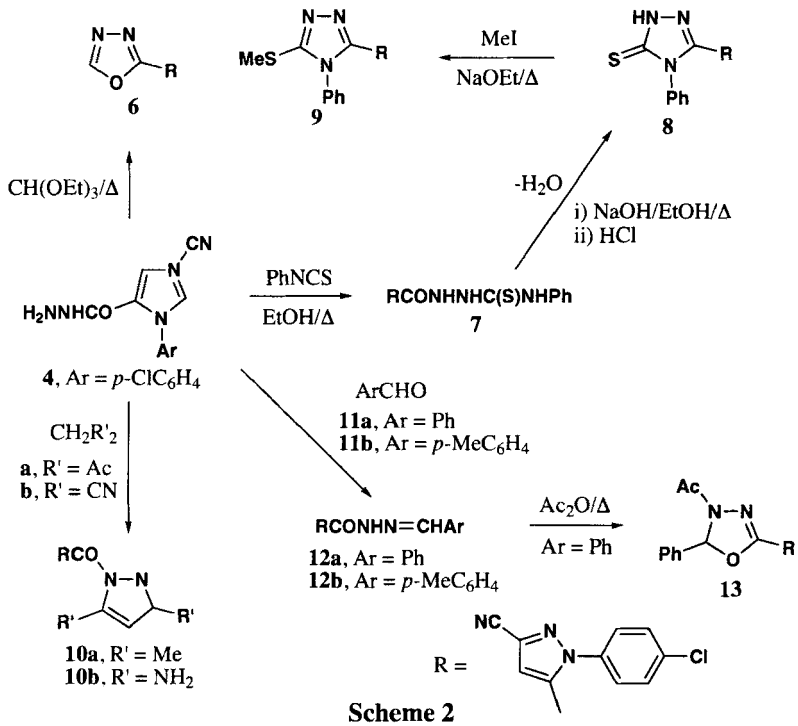
The starting 2-*p*-chlorophenylhydrazono-2-cyanoacetaldehyde (**1**) and 5-acetylpyrazole-3-carbonitrile **3c** were prepared as previously described.[36,38] Interaction of compound **1** with ethyl chloroacetate (**2a**) or chloroacetamide (**2b**), in the presence of an excess of potassium carbonate, afforded the corresponding 1-arylpyrazole-3-carbonitriles **3a,b**, respectively (*Scheme 1*). Confirmation of the proposed structure **3** was based on analytical and spectral data. In the case of **3a**, the IR spectrum indicated the presence of peaks at 2234 cm^{-1} (CN) and at 1724 cm^{-1} (CO). Its ^1H NMR spectrum displayed a triplet at δ 1.43 (3H) and a quartet at δ 4.26 (2H) corresponding to the ethyl ester group, as well as a singlet at δ 6.31 (1H) assigned to the hydrogen attached to C_4 of the pyrazole ring, besides the expected multiplet for the aromatic protons. This approach represents a simple and convenient one-pot method for the synthesis of functionalized substituted pyrazoles, difficult to obtain by other methods.



Scheme 1

The reactivity of 5-substituted-arylcyanopyrazoles **3a-c** was studied in reactions with hydrazine hydrate and dimethylformamide dimethylacetal (DMFDMA). Thus, treatment of **3a** with excess hydrazine hydrate led to the formation of the hydrazide **4**, which was also obtained by refluxing **3b** in hydrazine hydrate. A similar hydrazinolysis of a carboxamide has been reported.[39] The acetyl group of pyrazole derivative **3c** reacted easily with DMFDMA to afford the *trans* dimethylaminoacryloylpyrazole derivative **5** whose structure was based on the ^1H NMR spectrum, that revealed the presence of olefinic protons at δ 5.94 (1H) and δ 8.53 (1H) as two doublets with a coupling constant of 15 Hz.

When compound **4** was treated with excess triethyl orthoformate, it produced the oxadiazole derivative **6** *via* loss of ethanol. On the other hand, interaction of **4** with phenyl isothiocyanate led to the formation of the phenylthiosemicarbazide derivative **7**. Refluxing of compound **7** in ethanolic sodium hydroxide solution gave the triazolethione derivative **8**. The absence of the CO absorption band in the IR spectrum of **8** as well as the disappearance of the resonance signals from protons of the two NH units and the appearance of only one D_2O-exchangeable singlet for the NH proton of the triazole ring in the ^1H NMR spectrum support structure **8**. Further proof of the thione structure **8** was obtained by subsequent treatment of **8** with methyl iodide in refluxing ethanolic sodium ethoxide solution to provide the 5-methylthiotriazole derivative **9** (*Scheme 2*).

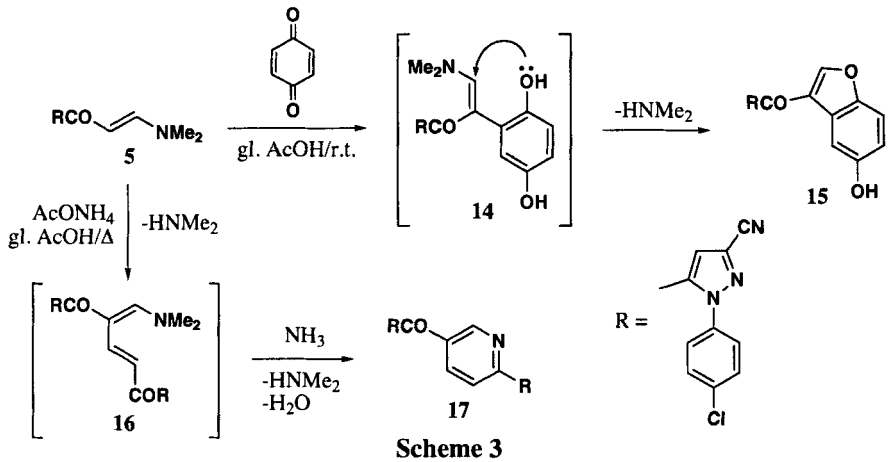


Scheme 2

The behavior of the carbohydrazide **4** towards acetylacetone and malononitrile was also investigated as a possible route for the synthesis of pyrazoles. With acetylacetone, the product was identified as 3,5-dimethylpyrazole derivative **10a**, while its 3,5-diamino analogue **10b** was the product of the reaction of **4** with malononitrile. These reactions proceeded in two stages, *viz.*, the initially formed hydroxy- or iminopyrazolines that subsequently aromatized to the final pyrazoles **10a,b**, *via* loss of water or through prototropic shift aromatization.[24] Elucidation of the proposed structure of the latter products was established on the basis of elemental analyses and spectral background in each case (*Experimental Section*).

The broad spectrum of pharmacological properties associated with *N*-arylidene hydrazide derivatives[40] encouraged us to synthesize new arylidene derivatives of potential biological interest. Thus, treatment of **4** with benzaldehyde (**11a**) or *p*-tolualdehyde (**11b**), in boiling ethanol, furnished the respective acyclic condensation products **12a,b**. Reaction of *N*-benzylidene hydrazide **12a** with acetic anhydride furnished the corresponding acetylated oxadiazole derivative **13**, formed most likely *via* intramolecular cyclization followed by subsequent *N*-acetylation (*Scheme 2*). Disappearance of the absorption band for the amidic carbonyl group upon formation of compound **13** is a preliminary indication for the cyclization process. Moreover, ^{1}H NMR spectrum of **13** was in accordance with the proposed structure of the synthesized compound (*Experimental Section*).

On the other hand, β-aminovinyl ketone **5** is highly reactive towards electrophilic reagents due to the presence of the electron rich C_2 of the ketoenamine moiety. Thus, compound **5** reacted with *p*-benzoquinone to yield a product of addition and dimethylamine elimination. The benzofuranoylpyrazole structure **15** was suggested for that product on the basis of its elemental analysis and spectral data. Appearance of only one absorption band for CO group, in the IR spectrum of **15**, is an indication for the formation of a cyclic structure. Moreover, besides the expected signals, its ^{1}H NMR spectrum revealed three singlets at δ 6.14 (1H), δ 8.85 (1H) and δ 10.03 (1H) attributed to the pyrazole-CH, furan-CH and OH protons, respectively. The formation of **15**, as illustrated (*Scheme 3*), may be rationalized *via* initial addition of electron rich C_2 in the enaminone **5** to the active double bond of *p*-benzoquinone, followed by subsequent

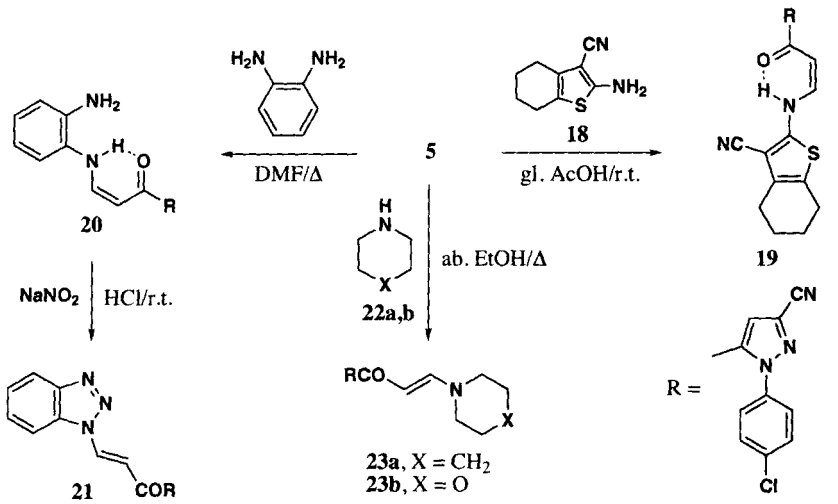


Scheme 3

enolization to afford the dihydroxy intermediate **14**. The latter underwent intramolecular ionic heterocyclization *via* nucleophilic attack by the OH function on the methylene CH, accompanied by 1,2-elimination with the release of dimethylamine, leading eventually to the benzofuran derivative **15**. This assumption is consistent with our earlier report[37] and with other reports[41,42] on the reactivity of enaminone towards 1,4-naphthoquinone with respect to the direct formation of naphthofuran. In support of this view, the reactivity and synthetic potential of the propenone derivative **5** for the formation of pyridine was further explored. As anticipated, the electron rich C_2 of the ketoenamine moiety in **5** proved to be also highly reactive towards self cyclocondensation. Thus, refluxing of **5** in acetic acid in the presence of ammonium acetate yielded the pyridine derivative **17**. The electron rich C_2 in one molecule of **5** adds to the electron deficient C_3 of another molecule, followed by dimethylamine elimination, to give the intermediate **16**. The latter cyclizes by the action of ammonia into product **17** (*Scheme 3*). IR and ^{1}H NMR spectra were informative in establishing the structure of pyridine derivative **17**. Its IR spectrum have absorption bands at 2232 and 2225 cm^{-1} corresponding to stretching vibrations of the two CN groups and a sharp absorption band for the CO stretching vibration at 1674 cm^{-1}. Signals for all the

protons are present in its ^{1}H NMR spectrum (*Experimental Section*). A similar mechanism has been suggested earlier by us to account for the self-condensation of enaminonitriles on reflux in acetic acid.[36]

Interaction of *trans* enaminone **5** with 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**18**)[30] afforded a product of condensation *via* the evolution of dimethylamine (*Scheme 4*). Accordingly, structure **19** for the *cis* enaminone could be established based on its ^{1}H NMR spectrum, which revealed the two vinyl protons as two doublets at δ 5.97 (1H) and δ 7.68 (1H) with a coupling constant value of 9 Hz, as required for such Z-coupled protons. The predominance of *cis* form is a result of the existence of intramolecular H-bonding which stabilizes this form. Incorporation of the benzotriazole moiety into pyrazole structure was achieved by converting of the *trans* enaminone **5** into its corresponding acyclic *cis* enaminone **20** followed by cyclization of the latter with sodium nitrite. Thus, compound **5** underwent facile nucleophilic substitution by *o*-phenylenediamine, resulting in the corresponding *cis* enaminone **20**. Closure of the triazole ring of the pyrazolylbenzotriazole system was carried out by diazotization and self coupling of the aminoacryloylpyrazole derivative **20** with sodium nitrite to form a bicyclic product, whose spectral and analytical data fully supported the proposed structure **21**. These results agree with a report in the literature[43] on a somewhat similar diazotization of aminocarboxamides with sodium nitrite.



Scheme 4

As an extension of such a synthetic route, the behavior of compound **5** towards secondary cycloaliphatic amines was also examined. Thus, nucleophilic displacement of the active dimethylamino group of **5** by piperidine (**22a**) or morpholine (**22b**), gave the corresponding derivatives of piperidino and morpholino **23a,b**, respectively (*Scheme 4*). Compounds **23a,b** were assigned the *E*-conformation on the bases of their ^{1}H NMR spectra (*Experimental Section*).

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. NMR spectra were obtained on a Varian Gemini 300 MHz spectrometer in DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts are expressed in δ ppm. EI mass spectra were recorded on a Finnigan MAT SSQ 710 at 70 eV. Compounds **1**, **3c**, and **18** were prepared as previously reported.[30,36,38]

Preparation of 5-Substituted-1-(4-chlorophenyl)-1*H*-pyrazole-3-carbonitriles (3a,b). General Procedure.- To a mixture of compound **1** (0.005 mol) and anhydrous potassium carbonate (0.01 mol) in dimethylformamide (20 mL), either α-chloroketone (**2a** or **2b**, 0.005 mol) was added. The mixture was heated at reflux for 5 h and then allowed to stand at room temperature overnight under stirring. The solvent was evaporated under reduced pressure and the residue poured over cold water and neutralized by hydrochloric acid. The resulting precipitate, in each case, was collected, dried and recrystallized from the appropriate solvent to give the pyrazoles **3a** (0.80 g; 58%) and **3b** (0.51 g; 41%), respectively.

Ethyl 1-(4-chlorophenyl)-3-cyano-1*H*-pyrazole-5-carboxylate (3a), yellow solid, mp. 142-143°C (EtOH); IR: 3051 (CH arom.), 2234 (CN), 1724 (C=O), 1612 (C=N) cm^{-1}; ^1H NMR: δ 1.43 (t, 3H, J = 7.0 Hz, Me ester), 4.26 (q, 2H, J = 7.0 Hz, CH_2 ester), 6.31 (s, 1H, CH pyrazole), 7.50-7.59 (m, 4H, Ar-H); MS: *m/z* (%) = 277 (M^+ +2, 12%), 275 (M^+, 28%).

Anal. Calcd for $C_{13}H_{10}ClN_3O_2$: C, 56.64; H, 3.66; Cl, 12.86; N, 15.24.

Found: C, 56.38; H, 3.47; Cl, 12.64; N, 14.99.

1-(4-Chlorophenyl)-3-cyano-1*H*-pyrazole-5-carboxamide (3b), pale yellow solid, mp. 191-193°C (EtOH-H_2O); IR: 3390, 3265 (NH_2), 3049 (CH arom.), 2235 (CN), 1656 (C=O), 1612 (C=N) cm^{-1}; ^1H NMR: δ 6.24 (s, 1H, CH pyrazole), 7.54-7.61 (m, 4H, Ar-H), 8.27 (s, 2H, NH_2, D_2O-exchangeable); MS: *m/z* (%) = 248 (M^+ +2, 15%), 246 (M^+, 34%).

Anal. Calcd for $C_{11}H_7ClN_4O$: C, 53.56; H, 2.86; Cl, 14.37; N, 22.71.

Found: C, 53.34; H, 2.70; Cl, 14.16; N, 22.59.

Preparation of 1-(4-Chlorophenyl)-3-cyano-1*H*-pyrazole-5-carbohydrazide (4). Method A.- To a solution of **3a** (0.005 mol) in ethanol (20 mL), hydrazine hydrate (1 mL, 0.02 mol) was added. The mixture was boiled under reflux for 6 h. The precipitate that formed after cooling at room temperature was collected by filtration and washed with ethanol and water. Recrystallization from EtOH/H_2O (4:1) gave the corresponding hydrazide derivative **4** (0.72 g; 55%), as a light brown solid, mp. 160-162°C; IR: 3370, 3215, 3162 ($NHNH_2$), 3055 (CH arom.), 2231 (CN), 1658 (C=O), 1611 (C=N) cm^{-1}; ^1H NMR: δ 4.70 (s, 2H, NH_2, D_2O-exchangeable), 6.21 (s, 1H, CH pyrazole), 7.48-7.57 (m, 4H, Ar-H), 9.65 (s, 1H, NH, D_2O-exchangeable); ^{13}C NMR: δ 112.3 (pyrazole C_4), 115.1 (CN), 121.2, 124.4, 129.7, 132.6, 136.9, 138.5 (arom. C and pyrazole $C_{3,5}$), 163.1 (C=O); MS: *m/z* (%) = 263 (M^+ +2, 5%), 261 (M^+, 16%).

Anal. Calcd for $C_{11}H_8ClN_5O$: C, 50.49; H, 3.08; Cl, 13.55; N, 26.76.

Found: C, 50.27; H, 2.91; Cl, 13.35; N, 26.49.

Method B.- Compound **3b** (0.01 mol) was added to hydrazine hydrate (10 mL, 0.2 mol) and the mixture was refluxed for 2 h. The mixture was poured onto water. The precipitate formed was washed with water, collected by filtration and purified by recrystallization from EtOH/H_2O to give a solid product (0.79 g; 30%) that was identical in all aspects (mp, mixed mp, and IR data) to **4** obtained by method A.

Preparation of 1-(4-Chlorophenyl)-5-[3-(dimethylamino)acryloyl]-1*H*-pyrazole-3-carbonitrile (5).- A mixture of **3c** (0.005 mol) and DMFDMA (0.006 mol) was refluxed in xylene (30 mL) for 12 h. The solvent was removed by evaporation under *vacuo*. The solid formed was collected, dried and recrystallized from EtOH to give the enaminoketone **5** (0.77 g; 51%), as a yellow solid, mp. 203-205°C; IR: 3055 (CH arom.), 2233 (CN), 1654 (C=O), 1614 (C=N) cm^{-1}; ^1H NMR: δ 2.93 (s, 6H, Me_2N), 5.94 (d, 1H, J = 15 Hz, 2-H olefin), 6.27 (s, 1H, CH pyrazole), 7.52-7.60 (m, 4H, Ar-H), 8.53 (d, 1H, J = 15 Hz, 3-H olefin); ^{13}C NMR: δ 44.9 (Me_2N), 93.4 (olefinic-*C*=C-N), 111.9 (pyrazole C_4), 113.8 (CN), 120.7, 124.6, 129.5, 132.8, 137.0, 139.2 (arom. C and pyrazole $C_{3,5}$), 155.4 (olefinic-C=*C*-N), 181.2 (C=O); MS: *m/z* (%) = 302 (M^+ +2, 18%), 300 (M^+, 57%).

Anal. Calcd for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; Cl, 11.79; N, 18.63.

Found: C, 59.66; H, 4.24; Cl, 11.65; N, 18.51.

Preparation of 1-(4-Chlorophenyl)-5-(1,3,4-oxadiazol-2-yl)-1*H*-pyrazole-3-carbonitrile (6).- A mixture of carbohydrazide **4** (0.002 mol) and triethyl orthoformate (10 mL) was refluxed for 8 h. The solvent was evaporated and residue was triturated with ethanol. The solid product obtained was collected, dried and recrystallized from EtOH to give the oxadiazole derivative **6** (0.48 g; 89%), as an orange solid, mp. 131-133°C; IR: 3059 (CH arom.), 2230 (CN), 1613 (C=N) cm^{-1}; ^1H NMR: δ 6.11 (s, 1H, CH pyrazole), 7.49-7.57 (m, 4H, Ar-H), 9.03 (s, 1H, CH oxadiazole); MS: *m/z* (%) = 273 (M^+ +2, 14%), 271 (M^+, 43%).

Anal. Calcd for $C_{12}H_6ClN_5O$: C, 53.05; H, 2.23; Cl, 13.05; N, 25.78.

Found: C, 52.83; H, 2.15; Cl, 12.92; N, 25.50.

Preparation of 1-[1-(4-Chlorophenyl)-3-cyano-1*H*-pyrazole-5-carbonyl]-4-phenylthiosemicarbazide (7).- To a solution of hydrazide **4** (0.005 mol) in ethanol (20 mL), phenyl isothiocyanate (0.005 mol) was added. The resulting mixture was heated at reflux for 5 h, then left aside to cool at room temperature. The solid that separated on cooling was collected by filtration, washed with ethanol and recrystallized from EtOH to give the thiosemicarbazide **7** (1.15 g; 58%), as a golden yellow solid, mp. 183-184°C; IR: 3316, 3260, 3187 (3NH), 3061 (CH arom.), 2228 (CN), 1664 (C=O), 1612 (C=N), 1251 (C=S) cm^{-1}; ^1H NMR: δ 6.22 (s, 1H, CH pyrazole), 6.84-7.65 (m, 9H, Ar-H), 9.61, 9.77 (2s, 2H, *NH*CS*NH*, D_2O-exchangeable), 10.48 (s, 1H, CO*NH*, D_2O-exchangeable).

Anal. Calcd for $C_{18}H_{13}ClN_6OS$: C, 54.48; H, 3.30; Cl, 8.93; N, 21.18; S, 8.08.

Found: C, 54.33; H, 3.14; Cl, 8.78; N, 20.97; S, 7.89.

Preparation of 1-(4-Chlorophenyl)-5-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-1*H*-pyrazole-3-carbonitrile (8).- Compound **7** (0.005 mol) was dissolved in ethanolic solution of sodium hydroxide (20 mL, 4%) and stirred at reflux for 5 h. The resulting solution was cooled and filtered. The filtrate was acidified with dilute hydrochloric acid and was kept aside for 1 h. The separated solid product was collected, washed repeatedly with water, dried and recrystallized from EtOH to give the thione derivative **8** (1.04 g; 55%), as a dark brown solid, mp. 198-199°C; IR: 3201 (NH), 3057 (CH arom.), 2228 (CN), 1610 (C=N), 1244 (C=S) cm^{-1}; ^1H NMR: δ 6.16 (s, 1H, CH pyrazole), 6.64-7.54 (m, 9H, Ar-H), 13.80 (s, 1H, triazoline NH, D_2O-exchangeable); ^{13}C NMR: δ 112.6 (pyrazole C_4), 114.5 (CN), 120.5, 124.1, 128.2, 128.8, 129.1, 129.7, 132.3, 133.5, 136.0, 137.4 (arom. and pyrazole carbons), 147.8 (triazoline C_3), 173.6 (C=S).

Anal. Calcd for $C_{18}H_{11}ClN_6S$: C, 57.07; H, 2.93; Cl, 9.36; N, 22.18; S, 8.46.

Found: C, 56.78; H, 2.81; Cl, 9.17; N, 21.96; S, 8.32.

Preparation of 1-(4-Chlorophenyl)-5-[5-(methylthio)-4-phenyl-4*H*-1,2,4-triazol-3-yl]-1*H*-pyrazole-3-carbonitrile (9).- To a solution of ethanolic sodium ethoxide [prepared by dissolving sodium metal (0.002 mol) in absolute ethanol (30 mL)], compound **8** (0.002 mol) was added and the solution was then heated under reflux for 10 min. The methyl iodide (0.0025 mol) was added and refluxing was continued for additional 2 h. The mixture was then cooled, poured onto cold water, neutralized with dilute hydrochloric acid (pH-7), whereby the product that separated out was collected, dried and recrystallized from 1,4-dioxane to give the methylthiotriazole derivative **9** (0.54 g; 69%), as a pale yellow solid, mp. 210-212 °C (AcOH-H_2O); IR: 3056 (CH arom.), 2226 (CN), 1610 (C=N) cm^{-1}; ^1H NMR: δ 2.65 (s, 3H, SMe), 6.18 (s, 1H, CH pyrazole), 7.19-7.57 (m, 9H, Ar-H).

Anal. Calcd for $C_{19}H_{13}ClN_6S$: C, 58.09; H, 3.34; Cl, 9.02; N, 21.39; S, 8.16.

Found: C, 57.84; H, 3.13; Cl, 8.91; N, 21.41; S, 7.95.

Preparation of 5-(3,5-Disubstituted-1*H*-pyrazole-1-carbonyl)-1-(4-chlorophenyl)-1*H*-pyrazole-3-carbonitriles (10a,b). General Procedure.- A mixture of equivalent amounts (0.002 mol) of **4** and either acetylacetone or malononitrile was refluxed in absolute ethanol (20 mL) for 5 h, concentrated to half its volume and was then allowed to cool. The precipitate so obtained was collected by filtration and recrystallized from the appropriate solvents to give the pyrazoles **10a** (0.51 g; 78%) and **10b** (0.49 g; 75%), respectively.

1-(4-Chlorophenyl)-5-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-1*H*-pyrazole-3-carbonitrile (10a), colorless solid, mp. 137-139°C (EtOH); IR: 3042 (CH arom.), 2223 (CN), 1659 (C=O), 1618 (C=N) cm^{-1}; ^1H NMR: δ 2.36 (s, 3H, Me), 2.65 (s, 3H, Me), 5.99 (s, 1H, CH pyrazole), 6.20 (s, 1H, CH pyrazole), 7.53-7.60 (m, 4H, Ar-H); MS: *m/z* (%) = 327 (M^+ +2, 10%), 325 (M^+, 21%).

Anal. Calcd for $C_{16}H_{12}ClN_5O$: C, 58.99; H, 3.71; Cl, 10.88; N, 21.50.

Found: C, 58.76; H, 3.54; Cl, 10.75; N, 21.23.

1-(4-Chlorophenyl)-5-(3,5-diamino-1*H*-pyrazole-1-carbonyl)-1*H*-pyrazole-3-carbonitrile (10b), yellow solid, mp. 128-129°C (EtOH/H_2O); IR: 3423, 3292 (NH_2), 3044 (CH arom.), 2223 (CN), 1660 (C=O), 1616 (C=N) cm^{-1}; ^1H NMR: δ 5.47 (s, br, 2H, NH_2, D_2O-exchangeable), 5.95 (s, 1H, CH pyrazole), 6.14 (s, 1H, CH pyrazole), 6.38 (s, br, 2H, NH_2, D_2O-exchangeable), 7.51-7.59 (m, 4H, Ar-H).

Anal. Calcd for $C_{14}H_{10}ClN_7O$: C, 51.31; H, 3.08; Cl, 10.82; N, 29.92.

Found: C, 51.02; H, 2.89; Cl, 10.61; N, 29.67.

Preparation of *N'*-Arylidene-1-(4-chlorophenyl)-3-cyano-1*H*-pyrazole-5-carbohydrazides (12a,b). General Procedure.- To a solution of equimolar amounts (0.003 mol) of carbohydrazide **4** and the appropriate aromatic aldehyde **11a,b** in absolute ethanol (15 mL), a few drops of glacial acetic acid was added. The mixture was heated under reflux for 4 h. After cooling, the resulting solid products were collected by filtration and recrystallized from the appropriate solvents to give the arylidenes **12a** (0.81 g; 77%) and **12b** (0.69 g; 63%), respectively.

***N'*-Benylidene-1-(4-chlorophenyl)-3-cyano-1*H*-pyrazole-5-carbohydrazide (12a),** orange solid, mp. 188-189°C (AcOH); IR: 3183 (NH), 3048 (CH arom.), 2225 (CN), 1667 (C=O), 1627 (C=N) cm^{-1}; ^1H NMR: δ 6.20 (s, 1H, CH pyrazole), 7.52-7.87 (m, 9H, Ar-H), 8.37 (s, 1H, *CH*=N), 11.71 (s, 1H, NH, D_2O-exchangeable).

Anal. Calcd for $C_{18}H_{12}ClN_5O$: C, 61.81; H, 3.46; Cl, 10.14; N, 20.02.

Found: C, 61.53; H, 3.34; Cl, 9.95; N, 19.83.

1-(4-Chlorophenyl)-3-cyano-*N'*-(4-methylbenzylidene)-1*H*-pyrazole-5-carbohydrazide (12b), brown solid, mp. 175-178°C (1,4-dioxane); IR: 3172 (NH), 3043 (CH arom.), 2225 (CN), 1670 (C=O), 1624 (C=N) cm^{-1}; ^1H NMR: δ 2.29 (s, 3H, Ar-Me), 6.17 (s, 1H, CH pyrazole), 7.33-7.69 (m, 8H, Ar-H), 8.16 (s, 1H, *CH*=N), 11.56 (s, 1H, NH, D_2O-exchangeable).

Anal. Calcd for $C_{19}H_{14}ClN_5O$: C, 62.73; H, 3.88; Cl, 9.75; N, 19.25.

Found: C, 62.56; H, 3.62; Cl, 9.60; N, 19.06.

Preparation of 5-(4-Acetyl-5-phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1-(4-chlorophenyl)-1*H*-pyrazole-3-carbonitrile (13).- A solution of benzylidene derivative **12a** (0.002 mol) in acetic anhydride (10 mL) was bioled under reflux for 2 h. After the reaction mixture was attained room temperature, excess acetic anhydride was decomposed by water (2 mL) and the mixture was stirred for 30 min. The separated product was collected, washed with a solution of sodium hydrogen carbonate followed by water and then dried. The product was recrystallized from EtOH to give the corresponding *N*-acetyl derivative **13** (0.60 g; 76%), as a pale yellow solid, mp. 148-149°C; IR: 3045 (CH arom.), 2227 (CN), 1673 (C=O), 1630 (C=N) cm^{-1}; ^1H NMR: δ 2.23 (s, 3H, Me), 6.08 (s, 1H, CH pyrazole), 6.47 (s, 1H, CH oxadiazoline), 7.31-7.60 (m, 9H, Ar-H).

Anal. Calcd for $C_{20}H_{14}ClN_5O_2$: C, 61.31; H, 3.60; Cl, 9.05; N, 17.87.

Found: C, 61.04; H, 3.51; Cl, 8.86; N, 17.58.

Preparation of 1-(4-Chlorophenyl)-5-(5-hydroxybenzofuran-3-carbonyl)-1*H*-pyrazole-3-carbonitrile (15).- To a stirred solution of enaminone **5** (0.005 mol) in glacial acetic acid (30

mL), *p*-benzoquinone (0.005 mol) was added. Stirring lasted overnight at room temperature. The mixture was evaporated *in vacuo*, and the solid product obtained was collected by filtration and recrystallized from EtOH/DMF mixture to give the benzofuran derivative **15** (0.69 g; 38%), as a yellow solid, mp. > 300°C; IR: 3402 (OH), 3051 (CH arom.), 2236 (CN), 1701 (C=O), 1615 (C=N) cm^{-1}; ^1H NMR: δ 6.14 (s, 1H, CH pyrazole), 6.98-7.49 (m, 7H, Ar-H), 8.85 (s, 1H, CH furan), 10.03 (s, 1H, OH, D_2O-exchangeable); MS: *m/z* (%) = 365 (M^+ +2, 13%), 363 (M^+, 32%).

Anal. Calcd for $C_{19}H_{10}ClN_3O_3$: C, 62.74; H, 2.77; Cl, 9.75; N, 11.55.

Found: C, 62.49; H, 2.63; Cl, 9.57; N, 11.42.

Preparation of 3-[1-(4-Chlorophenyl)-3-cyano-1*H*-pyrazole-5-carbonyl]-6-[1-(4-chlorophenyl)-3-cyano-1*H*-pyrazol-5-yl]pyridine (17).- A stirred suspension of glacial acetic acid (20 mL) and ammonium acetate (0.005 mol), was treated with enaminone **5** (0.005 mol). The mixture was refluxed for 2 h after which it was cooled to room temperature. The material which separated upon cooling was isolated by filtration and recrystallized from EtOH/1,4-dioxane (2:1 v/v) to give the pyridine derivative **17** (0.87 g; 34%), as a light brown solid, mp. 265°C; IR: 3055 (CH arom.), 2232, 2225 (2CN), 1674 (C=O), 1612 (C=N) cm^{-1}; ^1H NMR: δ 6.10 (s, 1H, CH pyrazole), 6.25 (s, 1H, CH pyrazole), 7.50-7.61 (m, 8H, Ar-H), 8.22 (d, 1H, *J* = 8.5 Hz, pyridine H-4), 8.40 (d, 1H, *J* = 8.5 Hz, pyridine H-5), 9.05 (s, 1H, pyridine H-2); MS: *m/z* (%) = 513 (M^+ +4, 3%), 511 (M^+ +2, 11%), 509 (M^+, 29%).

Anal. Calcd for $C_{26}H_{13}Cl_2N_7O$: C, 61.19; H, 2.57; Cl, 13.89; N, 19.21.

Found: C, 60.94; H, 2.43; Cl, 13.61; N, 19.02.

Preparation of 1-(4-Chlorophenyl)-5-[3-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-ylamino)acryloyl]-1*H*-pyrazole-3-carbonitrile (19).- 2-Aminobenzothiophene derivative **18** (0.002 mol) was added to a stirred solution of enaminone **5** (0.002 mol) in glacial acetic acid (30 mL). Stirring was continued overnight at room temperature, then poured onto water (50 mL). The solid product obtained was recovered by filtration and purified by recrystallization from DMF to give the *N*-substituted aminobenzothiophene derivative **19** (0.60 g; 69%), as an orange solid, mp. 224-226°C; IR: 3338-3170 (NH), 3039 (CH arom.), 2236, 2220 (2CN), 1641 (C=O with H-bonding), 1611 (C=N) cm^{-1}; ^1H NMR: δ 1.72 (m, 4H, $2CH_2$), 2.76 (m, 4H, $2CH_2$), 5.97 (d, 1H, *J* = 9 Hz, 2-H olefin), 6.20 (s, 1H, CH pyrazole), 7.50-7.57 (m, 4H, Ar-H), 7.68 (d, 1H, *J* = 9 Hz, 3-H olefin), 11.63 (s, br, 1H, NH, D_2O-exchangeable); MS: *m/z* (%) = 435 (M^+ +2, 21%), 433 (M^+, 65%).

Anal. Calcd for $C_{22}H_{16}ClN_5OS$: C, 60.90; H, 3.72; Cl, 8.17; N, 16.14; S, 7.39.

Found: C, 60.74; H, 3.62; Cl, 7.97; N, 15.88; S, 7.25.

Preparation of 5-[3-(2-Aminophenylamino)acryloyl]-1-(4-chlorophenyl)-1*H*-pyrazole-3-carbonitrile (20).- Equimolar amounts (0.003 mol) of **5** and *o*-phenylenediamine in dimethylformamide (15 mL) were refluxed for 12 h then poured over cold water. The precipitated solid was separated by filtration and purified by recrystallization from EtOH to give the acryloylpyrazole derivative **20** (0.85 g; 78%), as a yellow solid, mp. 235-237°C; IR: 3455-3321 (NH_2, NH),

3042 (CH arom.), 2231 (CN), 1638 (C=O with H-bonding), 1611 (C=N) cm^{-1}; ^1H NMR: δ 4.13 (s, 2H, NH_2, D_2O-exchangeable), 6.13 (s, 1H, CH pyrazole), 6.32 (d, 1H, *J* = 9 Hz, 2-H olefin), 6.59-7.61 (m, 8H, Ar-H), 7.76 (d, 1H, *J* = 9 Hz, 3-H olefin), 12.05 (s, br, 1H, NH, D_2O-exchangeable).

Anal. Calcd for $C_{19}H_{14}ClN_5O$: C, 62.73; H, 3.88; Cl, 9.75; N, 19.25.

Found: C, 62.64; H, 3.67; Cl, 9.56; N, 18.98.

Preparation of 5-[3-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)acryloyl]-1-(4-chlorophenyl)-1*H*-pyrazole-3-carbonitrile (21).- To a cold (0-5°C) solution of **20** (0.002 mol) in dilute hydrochloric acid (10 mL, 50%), was added dropwise with stirring a cold solution of sodium nitrite (0.69 g, in 10 mL of water). Stirring was continued at this temperature for 20 minutes, then it was left to stand at room temperature for 3 h. The solid product thus formed was isolated by filtration and recrystallized from EtOH/1,4-dioxane mixture (1:1) to give the triazole derivative **21** (0.61 g; 82%), as a light brown solid, mp. 158-159°C; IR: 3044 (CH arom.), 2231 (CN), 1660 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR: δ 6.18 (s, 1H, CH pyrazole), 6.64 (d, 1H, *J* = 13 Hz, 2-H olefin), 7.20-7.86 (m, 8H, Ar-H), 8.38 (d, 1H, *J* = 13 Hz, 3-H olefin); MS: *m/z* (%) = 376 (M^+ +2, 11%), 374 (M^+, 25%).

Anal. Calcd for $C_{19}H_{11}ClN_6O$: C, 60.89; H, 2.96; Cl, 9.46; N, 22.42.

Found: C, 60.64; H, 3.01; Cl, 9.21; N, 22.18.

Preparation of 5-(3-Substituted-acryloyl)-1-(4-chlorophenyl)-1*H*-pyrazole-3-carbonitriles (23a,b). General Procedure.- A mixture of compound **5** (0.002 mol) and either piperidine (**22a**) or morpholine (**22b**) (0.004 mol) in absolute ethanol (20 mL) was refluxed for 10 h. The mixture was then cooled, poured onto ice/water mixture, and neutralized with acetic acid (pH-7). The resulting solid product so formed, in each case, was collected by filtration, dried and recrystallized from the appropriate solvents to give **23a** (0.59 g; 86%) and **23b** (0.53 g; 78%), respectively.

1-(4-Chlorophenyl)-5-[3-(piperidin-1-yl)acryloyl]-1*H*-pyrazole-3-carbonitrile (23a), golden yellow solid, mp. 152-153°C (MeOH/H_2O); IR: 3051 (CH arom.), 2233 (CN), 1654 (C=O), 1614 (C=N) cm^{-1}; ^1H NMR: δ 1.56 (m, 6H, $3CH_2$), 3.39 (m, 4H, $[CH_2]_2N$), 5.84 (d, 1H, *J* = 14 Hz, 2-H olefin), 6.17 (s, 1H, CH pyrazole), 7.50-7.59 (m, 4H, Ar-H), 7.83 (d, 1H, *J* = 14 Hz, 3-H olefin).

Anal. Calcd for $C_{18}H_{17}ClN_4O$: C, 63.44; H, 5.03; Cl, 10.40; N, 16.44.

Found: C, 63.16; H, 4.87; Cl, 10.24; N, 16.28.

1-(4-Chlorophenyl)-5-(3-morpholinoacryloyl)-1*H*-pyrazole-3-carbonitrile (23b), pale yellow solid mp. 167-168°C (MeOH); IR: 3055 (CH arom.), 2232 (CN), 1654 (C=O), 1612 (C=N) cm^{-1}; ^1H NMR: δ 3.41 (m, 4H, $[CH_2]_2N$), 3.73 (m, 4H, $[CH_2]_2O$), 5.89 (d, 1H, *J* = 13 Hz, 2-H olefin), 6.15 (s, 1H, CH pyrazole), 7.52-7.60 (m, 4H, Ar-H), 7.91 (d, 1H, *J* = 13 Hz, 3-H olefin).

Anal. Calcd for $C_{17}H_{15}ClN_4O_2$: C, 59.57; H, 4.41; Cl, 10.34; N, 16.34.

Found: C, 59.41; H, 4.24; Cl, 10.15; N, 16.06.

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