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Note

Reaction of 3-aminocyclohex-2-en-1-ones with arylidenemalononitriles: Synthesis, characterization and antimicrobial activity of some new quinoline bearing pyrazole nucleus

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A new series of quinoline bearing pyrazole nucleus **D_{1-36}** have been prepared in one pot by condensing various arylidenemalononitriles **A_{1-3}** and 3-aminocyclohex-2-en-1-ones **B_{1-12}** in alcohol and in the presence of catalytic amount of piperidine. All the compounds have been characterized by their percentage yield, melting point, elemental analysis, ^{1}H NMR and ^{13}C NMR spectra and IR spectra. These compounds have been screened for their antimicrobial activities.

Keywords: Quinoline bearing pyrazole nucleus, 3-amino-cyclohex-2-en-1-ones, arylidenemalononitriles and antimicrobial activity.

Quinolines are the versatile nitrogen containing heterocyclic compounds. The quinoline derivatives have remarkable pharmacological activity and widely used in the field of antimalarial drugs. Aminoquinolines are found to be associated with a number of biological activities, viz. antidepressant[1], antiviral[2,3] and antiherpetic[4] agents.

Pyrazole and its synthetic analogues have been found to exhibit industrial, agricultural and biological applications[5,6]. Pyrazole derivatives exhibit broad spectrum of therapeutic activity like antitumor[7], antiulcer[8], antiparasitic[9] etc. Keeping this in view, it was considered of interest to synthesize some new derivatives of quinoline bearing pyrazole nucleus.

Results and Discussion

Reaction between various 2-((5-chloro-1-(3 or 4 substitutedphenyl)-3-methyl-1*H*-pyrazol-4-yl)methyl-ene)malanonitrile[10] **A_{1-3}** and 3-amino-cyclohex-2-en-1-ones[11] **B_{1-12}** in alcohol in the presence of catalytic amount of piperidine gave cyclized product of quinoline bearing pyrazole nucleus **D_{1-36}** in good yield (80-90) **(Table I)**.

Quinolines type compounds **D_{1-36}** **(Table I)** are synthesized by a base induced cyclocondensation of various cyclic enaminones **B_{1-12}**. In this process, the pyridine ring is constructed by formation of acyclic alkylated Michael adduct **C** which affords the final products **D_{1-36}** upon cyclization **(Scheme I)**.

Evaluation of antimicrobial activity

The *in vitro* antimicrobial activity was carried out against 24 hr old cultures of three bacteria and three fungi by disc diffusion method[12, 13]. Compounds **D_{1-36}** has been tested for their antibacterial activity against *Escherichia coli* as Gram-negative bacteria and *Bacillus subtillis* and *Staphylococcus aureus* as Gram-positive bacteria and antifungal activity against *Aspergillus niger* and *Fuserium oxysporum* and *Rhizopus oryzae*. Ciprofloxacin, ampicillin and griseofulvin were used as standards for comparison of antibacterial and antifungal activity respectively. Inhibition was recorded by measuring the diameter of zones (mm) at the end of 24 hr. for bacteria at 35°C and 48 hr. for fungus at 28°C.

The antimicrobial study revealed that compounds **D_6, D_{12}, D_{17}, D_{23}, D_{24}, D_{30}** and **D_{35}** show good activity against gram positive bacteria *S.aureus* and compounds **D_6, D_{15}, D_{18}, D_{27}, D_{35}** show good activity against gram positive bacteria *B.substillis*. Compounds **D_7, D_9, D_{13}, D_{16}, D_{26}, D_{28}, D_{31}** and **D_{36}** show good activity against gram negative bacteria *E. coli* compared to the standard drug ampicillin. The antifungal study revealed that the compounds **D_2, D_7, D_8, D_{16}, D_{30}** and **D_{35}** show good activity against *Aspergillus niger,* compounds **D_6, D_9, D_{23}, D_{26}, D_{29}** and **D_{32}** show good activity against *Fuserium oxysporum* and compounds **D_5, D_{11}, D_{13}, D_{17}, D_{20}, D_{23}, D_{25}, D_{28}, D_{31}, D_{32}** and **D_{36}** show good activity against *Rhizopus oryzae* compared to the standard drug griseofulvin.

Experimental Section

All the melting points are uncorrected and expressed in °C. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds was carried out by TLC. TLC was runned using TLC aluminum sheet silica gel 60 F_{254} (Merck).

Table I — Physical and analytical characterization data of compounds $\mathbf{D_{1\text{-}36}}$

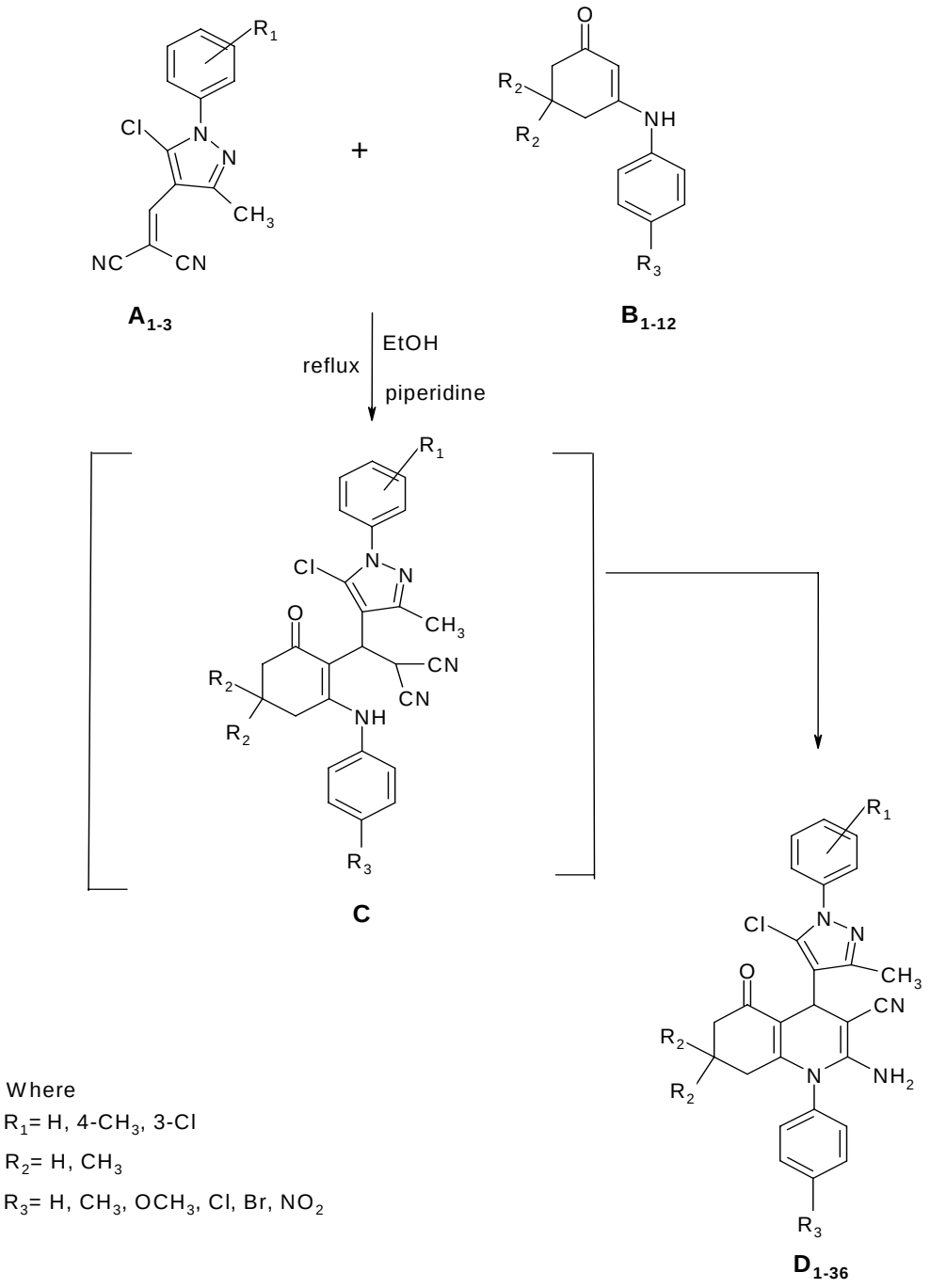
Compd	R_1	R_2	R_3	m.p.(°C) (Yield %)	Mol. Formula (Mol. Wt)	Compd	R_1	R_2	R_3	m.p.(°C) (Yield %)	Mol. Formula (Mol. Wt)
D_1	H	H	H	279 (85)	$C_{26}H_{22}ClN_5O$ (455.9)	**D_{19}**	H	CH_3	H	282 (86)	$C_{28}H_{26}ClN_5O$ (484.0)
D_2	H	H	CH_3	282 (82)	$C_{27}H_{24}ClN_5O$ (485.9)	**D_{20}**	H	CH_3	CH_3	283 (83)	$C_{29}H_{28}ClN_5O$ (498.0)
D_3	H	H	OCH_3	283-85 (81)	$C_{27}H_{24}ClN_5O_2$ (485.9)	**D_{21}**	H	CH_3	OCH_3	288 (80)	$C_{29}H_{28}ClN_5O_2$ (514.0)
D_4	H	H	Cl	290-92 (78)	$C_{26}H_{21}Cl_2N_5O$ (490.4)	**D_{22}**	H	CH_3	Cl	292-94 (78)	$C_{28}H_{25}Cl_2N_5O$ (518.4)
D_5	H	H	Br	287 (86)	$C_{26}H_{21}BrClN_5O$ (534.8)	**D_{23}**	H	CH_3	Br	289 (88)	$C_{28}H_{25}BrClN_5O$ (562.9)
D_6	H	H	NO_2	279 (88)	$C_{26}H_{21}ClN_{6O3}$ (500.9)	**D_{24}**	H	CH_3	NO_2	275 (85)	$C_{28}H_{25}ClN_6O_3$ (529.0)
D_7	CH_3	H	H	283 (85)	$C_{27}H_{24}ClN_5O$ (469.9)	**D_{25}**	CH_3	CH_3	H	276 (81)	$C_{29}H_{28}ClN_5O$ (498.0)
D_8	CH_3	H	CH_3	287 (82)	$C_{28}H_{26}ClN_5O$ (484.0)	**D_{26}**	CH_3	CH_3	CH_3	283 (80)	$C_{30}H_{30}ClN_5O$ (512.0)
D_9	CH_3	H	OCH_3	291 (80)	$C_{28}H_{26}ClN_5O_2$ (500.0)	**D_{27}**	CH_3	CH_3	OCH_3	290 (88)	$C_{30}H_{30}ClN_5O_2$ (528.0)
D_{10}	CH_3	H	Cl	284-86 (78)	$C_{27}H_{23}Cl_2N_5O$ (504.4)	**D_{28}**	CH_3	CH_3	Cl	281-83 (78)	$C_{29}H_{27}Cl_2N_5O$ (532.4)
D_{11}	CH_3	H	Br	278 (85)	$C_{27}H_{23}BrClN_5O$ (584.7)	**D_{29}**	CH_3	CH_3	Br	276 (83)	$C_{29}H_{27}BrClN_5O$ (576.9)
D_{12}	CH_3	H	NO_2	285 (89)	$C_{27}H_{23}ClN_6O_3$ (514.9)	**D_0**	CH_3	CH_3	NO_2	270 (88)	$C_{29}H_{27}ClN_6O_3$ (543.0)
D_{13}	Cl	H	H	275 (87)	$C_{26}H_{21}Cl_2N_5O$ (490.4)	**D_{31}**	Cl	CH_3	H	284 (81)	$C_{28}H_{25}Cl_2N_5O$ (518.4)
D_{14}	Cl	H	CH_3	286 (79)	$C_{27}H_{23}Cl_2N_5O$ (504.4)	**D_{32}**	Cl	CH_3	CH_3	272 (75)	$C_{29}H_{27}Cl_2N_5O_2$ (532.4)
D_{15}	Cl	H	OCH_3	277-79 (81)	$C_{27}H_{23}Cl_2N_5O_2$ (520.4)	**D_{33}**	Cl	CH_3	OCH_3	268 (80)	$C_{29}H_{27}Cl_2N_5O_2$ (548.4)
D_{16}	Cl	H	Cl	272 (82)	$C_{26}H_{20}Cl_3N_5O$ (524.8)	**D_{34}**	Cl	CH_3	Cl	269 (76)	$C_{28}H_{24}C_{l3}N_5O$ (552.9)
D_{17}	Cl	H	Br	272 (82)	$C_{26}H_{20}BrCl_2N_5O$ (569.2)	**D_{35}**	Cl	CH_3	Br	276 (85)	$C_{28}H_{27}BrCl_2N_5O$ (597.2)
D_{18}	Cl	H	NO_2	282 (84)	$C_{26}H_{21}ClN_6O_3$ (535.9)	**D_{36}**	Cl	CH_3	NO_2	286 (89)	$C_{28}H_{24}ClN_6O_3$ (565.4)

* All the compounds gave satisfactory C, H, N analysis.

Elemental analysis (% C, H, N) was carried out by Perkin Elmer 2400 CHN analyzer. IR spectra of all the compounds have been recorded on a Schimadzu FT-IR 8401 spectrophotometer in KBr. The ^{1}H NMR and ^{13}C NMR spectra have been recorded on a Bruker AC 400F (400MHz) instrument using TMS as internal standard in DMSO-d_6 as a solvent. Chemical shifts are reported in parts per million (ppm). Mass Spectra were scanned on a Schimadzu Lcms 2010 spectrometer.

Preparation of 2-amino-4-(5-chloro-3-methyl-1-(3 or 4-subtitutedphenyl)-1*H*-pyrazol-4-yl)-1-(4-substituted phenyl)-7, 7-disubstituted-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile $D_{1\text{-}36}$

General procedure: A mixture of 3-amino-cyclohex-2-en-1-ones **($B_{1\text{-}12}$)** (0.01mole), 2-((5-chloro-1-(3 or 4-substitutedphenyl)-3-methyl-1*H*-pyrazol-4-yl)methylene)malanonitrile **($A_{1\text{-}3}$)** (0.01mole) and piperidine (3 drops) in ethanol (10 mL) was refluxed



Scheme I

with continuous stirring. The reaction was monitored by TLC, after the completion of reaction, it was cooled to room temperature and stirred for 10-15 min; the resulting solid mass was filtered, washed with small amount of ethanol and dried. The crude product was purified by leaching in equimolar mixture of chloroform and methanol to obtain the pure solid sample.

2-Amino-4-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile D_1: IR (KBr): 3445-3310 (NH_2-stretching), 2180 (CN- stretching), 1660 cm^{-1} (C=O-stretching); ^1H NMR (DMSO-d_6): δ 2.23(s, 3H, CH_3), 1.80-2.46(m, 6H, 3 × CH_2), 4.60(s, 1H, CH), 5.45(s, 2H, NH_2), 7.29-7.60(m, 10H, Ar-H); ^{13}C NMR: δ 21.00(CH_3), 21.20, 27.41, 36.40((-CH_2)$_3$), 28.32

(-*C*H-), 57.80(*C*-CN), 195.43(*C*=O), 109.50, 115.15, 122.06, 124.70, 124.85, 126.36, 130.48, 132.59, 134.74, 134.89, 135.30, 136.00, 137.26, 141.25, 147.92, 149.65, 151.41, 153.18(*C*-Ar); MS: *m/z* 456.1 (M^+).

2-Amino-4-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile D_6: IR (KBr): 3440-3315 (NH_2- stretching), 2186 (CN- stretching), 1665 cm^{-1} (C=O- stretching); ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H, CH_3), 1.85-2.55(m, 6H, 3 × CH_2), 4.65(s, 1H, CH), 5.60(s, 2H, NH_2), 7.45-8.38(m, 9H, Ar-H); ^{13}C NMR: δ 13.03(*C*H_3), 21.27, 27.66, 36.45((-*C*H_2)$_3$), 28.52(-*C*H-), 58.40(*C*-CN), 195.58(*C*=O), 109.79, 115.32, 121.75, 122.12, 124.85, 125.05, 125.71, 128.34, 129.55, 132.59, 138.35, 142.39, 146.06, 148.26, 148.43, 151.19, 152.56(*C*-Ar); MS: *m/z* 501.1 (M^+).

2-Amino-4-(5-chloro-3-methyl-1-*p*-tolyl-1*H*-pyrazol-4-yl)-1-(4-chlorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile D_{10}: IR (KBr): 3450-3320 (NH_2- stretching), 2190 (CN- stretching), 1655 cm^{-1} (C=O- stretching); ^{1}H NMR (DMSO-d_6): δ 1.63 (s, 3H, CH_3), 2.19(s, 3H, CH_3), 1.80-2.50(m, 6H, 3 × CH_2), 4.62(s, 1H, CH), 5.49(s, 2H, NH_2), 7.31-7.62(m, 8H, Ar-H); ^{13}C NMR: δ 12.98, 21.09((*C*H_3)$_2$), 21.22, 27.50, 36.42((-*C*H_2)$_3$), 28.37(-*C*H-), 57.84(*C*-CN), 195.54(*C*=O), 109.57, 122.01, 124.72, 124.91, 129.98, 130.59, 132.48, 134.84, 134.92, 135.35, 135.99, 137.86, 147.95, 151.44, 153.24(*C*-Ar); MS: *m/z* 504.1 (M^+).

2-Amino-4-(5-chloro-1-(3-cholrophenyl)-3-methyl-1*H*-pyrazol-4-yl)-1-(4-methoxyphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile D_{15}: IR (KBr): 3442-3330 (NH_2- stretching), 2182 (CN-stretching), 1668 cm^{-1} (C=O-stretching); ^{1}H NMR (DMSO-d_6): δ 2.17 (s, 3H, CH_3), δ 3.81(s, 3H, OCH_3), 1.65-2.34(m, 6H, 3 × CH_2), 4.64(s, 1H, CH), 5.29 (s, 2H, NH_2), 7.10-7.65(m, 8H, Ar-H); ^{13}C NMR: δ 12.94(*C*H_3), 21.19, 27.54, 36.41((-*C*H_2)$_3$), 28.31 (-*C*H-), 55.96(O*C*H_3), 57.84(*C*-CN), 195.47(*C*=O), 109.24, 115.89, 121.55, 122.97, 123.42, 124.52, 124.98 128.14, 128.68, 131.28, 133.81, 139.49, 141.45, 148.97, 151.85, 154.04, 160.27(*C*-Ar) ; MS: *m/z* 520.1 (M^+).

2-Amino-4-(5-chloro-3-methyl-1-*p*-tolyl-1*H*-pyrazol-4-yl)-1-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile D_{28}: IR (KBr): 3442-3333 (NH_2- stretching), 2165 (CN-stretching), 1662 cm^{-1} (C=O- stretching); ^{1}H NMR (DMSO-d_6): δ 0.80(s, 3H, CH_3), 0.86(s, 3H, CH_3), 1.63(s, 3H, CH_3), 1.74 -2.36(m, 4H, 2 × CH_2), 2.15 (s, 3H, CH_3), 4.62(s, 1H, CH), 5.30(s, 2H, NH_2), 7.10-7.63(m, 8H, Ar-H); ^{13}C NMR: δ 12.94, 20.60((*C*H_3)$_2$), 26.17, 27.50(C-(*C*H_3)$_2$), 32.37(*C*-(CH$_3$)$_2$), 36.94, 40.62 ((-*C*H_2)$_2$), 29.60(-*C*H-), 57.39(*C*-CN), 195.45 (*C*=O), 109.37, 114.40, 122.03, 123.66, 124.56, 125.22, 126.86, 127.98 128.59, 131.23, 132.99, 139.78, 148.93, 150.07, 151.88, 152.39, 158.34 (*C*-Ar); MS: *m/z* 532.1 (M^+).

2-Amino-4-(5-chloro-1-(3-chlorophenyl)-3-methyl-1*H*-pyrazol-4-yl)-1-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile D_{33}: IR (KBr): 3458-3325 (NH_2- stretching), 2179 (CN- stretching), 1642 cm^{-1} (C=O- stretching); ^{1}H NMR (DMSO-d_6): δ 0.80(s, 3H, CH_3), 0.89(s, 3H, CH_3), 1.74 -2.15(m, 4H, 2 × CH_2), 2.36(s, 3H, CH_3), 3.83(s, 3H, OCH_3), 4.60(s, 1H, CH), 5.27(s, 2H, NH_2), 7.10-7.63(m, 8H, Ar-H); ^{13}C NMR: δ 12.94 (CH_3), 26.97, 27.58 (C-(*C*H_3)$_2$), 32.17 (*C*-(CH$_3$)$_2$), 40.94, 49.62((-*C*H_2)$_2$), 55.97(O*C*H_3), 29.51(-*C*H-), 57.32(*C*-CN), 195.60(*C*=O), 108.47,115.60, 121.93, 123.36, 124.45, 125.02, 127.76, 128.20 128.55, 131.33, 133.85, 139.45, 149.05, 149.67, 151.71, 152.09, 160.24(*C*-Ar); MS: *m/z* 548.1 (M^+).

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