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 D1-36 have been prepared in one pot by condensing various arylidenemalononitriles A1-3 and 3-aminocyclohex-2-en-1-ones B1-12 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, 1H NMR and 13C NMR spectra and IR spectra. These compounds have been screened for their antimicrobial activities.

Keywords: Quinoline bearing pyrazole nucleus, 3-aminocyclohex-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. Aminquinolines are found to be associated with a number of biological activities, viz. antidepressant1, antiviral2,3 and antitherapeutic4 agents.

Pyrazole and its synthetic analogues have been found to exhibit industrial, agricultural and biological applications5,6. Pyrazole derivatives exhibit broad spectrum of therapeutic activity like antitumor7, antiulcer8, antiparasitic9 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-1H-pyrazol-4-yl)methylene)malononitrile A1,3 and 3-aminocyclohex-2-en-1-ones B1,12 in alcohol in the presence of catalytic amount of piperidine gave cyclized product of quinoline bearing pyrazole nucleus D1-36 in good yield (80-90) (Table I).

Note

Quinolines type compounds D1-36 (Table I) are synthesized by a base induced cyclocondensation of various cyclic enamines B1,12. In this process, the pyridine ring is constructed by formation of acyclic alkylated Michael adduct C which affords the final products D1-36 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 method12,13. Compounds D1-36 has been tested for their antibacterial activity against Escherichia coli as Gram-negative bacteria and Bacillus subtilis and Staphylococcus aureus as Gram-positive bacteria and antifungal activity against Aspergillus niger and Fusarium 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 D6, D12, D17, D23, D24, D30 and D35 show good activity against gram positive bacteria S.aureus and compounds D6, D15, D18, D27, D35 show good activity against gram positive bacteria B.subtilis. Compounds D7, D8, D13, D16, D26, D28, D31 and D36 show good activity against gram negative bacteria E. coli compared to the standard drug ampicillin. The antifungal study revealed that the compounds D3, D5, D9, D16, D30 and D35 show good activity against Aspergillus niger, compounds D6, D8, D23, D26, D29 and D32 show good activity against Fusarium oxysporum and compounds D5, D11, D13, D17, D20, D23, D25, D28, D11, D32 and D36 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 F254 (Merck).
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.

**Table I** — Physical and analytical characterization data of compounds D$_{1-36}$

| 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$_5$O (455.9) | D$_{19}$ | H     | CH$_3$ | H     | 282 (86)            | C$_{26}$H$_{22}$ClN$_5$O (454.0) |
| D$_2$ | H     | H     | CH$_3$ | 282 (82)            | C$_{27}$H$_{25}$ClN$_5$O (485.9) | D$_{20}$ | H     | CH$_3$ | CH$_3$ | 283 (83)            | C$_{28}$H$_{25}$ClN$_5$O (498.0) |
| D$_3$ | H     | H     | OCH$_3$ | 283-85 (81)         | C$_{27}$H$_{25}$ClN$_5$O$_2$ (485.9) | D$_{21}$ | H     | CH$_3$ | OCH$_3$ | 288 (80)            | C$_{28}$H$_{25}$ClN$_5$O$_2$ (514.0) |
| D$_4$ | H     | H     | Cl    | 290-92 (78)         | C$_{26}$H$_{21}$Cl$_2$N$_5$O (490.4) | D$_{22}$ | H     | CH$_3$ | Cl    | 292-94 (78)         | C$_{28}$H$_{25}$Cl$_2$N$_5$O (518.4) |
| D$_5$ | H     | H     | Br    | 287 (86)            | C$_{26}$H$_{21}$BrClN$_5$O (534.8) | D$_{23}$ | H     | CH$_3$ | Br    | 289 (88)            | C$_{28}$H$_{25}$BrClN$_5$O (562.9) |
| D$_6$ | H     | H     | NO$_2$ | 279 (88)            | C$_{26}$H$_{21}$BrClN$_5$O$_2$ (500.9) | D$_{24}$ | H     | CH$_3$ | NO$_2$ | 275 (85)            | C$_{28}$H$_{25}$BrClN$_5$O$_3$ (529.0) |
| D$_7$ | CH$_3$ | H     | H     | 283 (85)            | C$_{27}$H$_{24}$ClN$_5$O (469.9) | D$_{25}$ | C     | CH$_3$ | H     | 276 (81)            | C$_{29}$H$_{28}$ClN$_5$O (498.0) |
| D$_8$ | CH$_3$ | H     | CH$_3$ | 287 (82)            | C$_{28}$H$_{26}$ClN$_5$O (484.0) | D$_{26}$ | C     | CH$_3$ | CH$_3$ | 283 (80)            | C$_{30}$H$_{30}$ClN$_5$O (512.0) |
| D$_9$ | CH$_3$ | H     | OCH$_3$ | 291 (80)            | C$_{27}$H$_{23}$ClN$_5$O$_2$ (500.0) | D$_{27}$ | C     | CH$_3$ | OCH$_3$ | 290 (88)            | C$_{29}$H$_{27}$ClN$_5$O$_2$ (528.0) |
| D$_{10}$ | CH$_3$ | H     | Cl    | 284-86 (78)         | C$_{27}$H$_{23}$Cl$_2$N$_5$O (504.4) | D$_{28}$ | C     | CH$_3$ | Cl    | 281-83 (78)         | C$_{29}$H$_{27}$Cl$_2$N$_5$O (532.4) |
| D$_{11}$ | CH$_3$ | H     | Br    | 278 (85)            | C$_{27}$H$_{23}$BrClN$_5$O (584.7) | D$_{29}$ | C     | CH$_3$ | Br    | 276 (83)            | C$_{29}$H$_{27}$BrClN$_5$O (576.9) |
| D$_{12}$ | CH$_3$ | H     | NO$_2$ | 285 (89)            | C$_{27}$H$_{23}$ClN$_5$O$_2$ (514.9) | D$_0$   | C     | CH$_3$ | NO$_2$ | 270 (88)            | C$_{30}$H$_{28}$ClN$_5$O$_2$ (543.0) |
| D$_{13}$ | Cl    | H     | H     | 275 (87)            | C$_{26}$H$_{22}$Cl$_2$N$_5$O (490.4) | D$_{31}$ | Cl    | CH$_3$ | H     | 284 (81)            | C$_{28}$H$_{26}$Cl$_2$N$_5$O (518.4) |
| D$_{14}$ | Cl    | H     | CH$_3$ | 286 (79)            | C$_{27}$H$_{25}$ClN$_5$O$_2$ (504.4) | D$_{32}$ | Cl    | CH$_3$ | CH$_3$ | 272 (75)            | C$_{29}$H$_{28}$Cl$_2$N$_5$O (532.4) |
| D$_{15}$ | Cl    | H     | OCH$_3$ | 277-79 (81)         | C$_{26}$H$_{21}$Cl$_2$N$_5$O$_2$ (520.4) | D$_{33}$ | Cl    | CH$_3$ | OCH$_3$ | 268 (80)            | C$_{28}$H$_{25}$Cl$_2$N$_5$O$_2$ (548.4) |
| D$_{16}$ | Cl    | H     | Cl    | 272 (82)            | C$_{26}$H$_{21}$BrClN$_5$O$_2$ (524.8) | D$_{34}$ | Cl    | CH$_3$ | Cl    | 269 (76)            | C$_{28}$H$_{25}$BrClN$_5$O$_2$ (552.9) |
| D$_{17}$ | Cl    | H     | Br    | 272 (82)            | C$_{26}$H$_{21}$BrClN$_5$O$_2$ (569.2) | D$_{35}$ | Cl    | CH$_3$ | Br    | 276 (85)            | C$_{28}$H$_{25}$BrClN$_5$O$_2$ (597.2) |
| D$_{18}$ | Cl    | H     | NO$_2$ | 282 (84)            | C$_{26}$H$_{21}$ClN$_6$O$_3$ (535.9) | D$_{36}$ | Cl    | CH$_3$ | NO$_2$ | 286 (89)            | C$_{28}$H$_{25}$ClN$_6$O$_3$ (565.4) |

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

Preparation of 2-amino-4-(5-chloro-3-methyl-1-(3 or 4-substitutedphenyl)-1H-pyrazol-4-yl)-1-(4-substituted phenyl)-7, 7-disubstituted-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile D$_{1-36}$

**General procedure:** A mixture of 3-amino-cyclohex-2-en-1-ones (B$_{1-12}$) (0.01mole), 2-((5-chloro-1-(3 or 4-substitutedphenyl)-3-methyl-1H-pyrazol-4-yl)methylene)malononitrile (A$_{1-3}$) (0.01mole) and piperidine (3 drops) in ethanol (10 mL) was refluxed...
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-1H-pyr azol-4-yl)-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile D₁: IR (KBr): 3445-3310 (NH₂-stretching), 2180 (CN-stretching), 1660 cm⁻¹ (C=O-stretching); ¹H NMR (DMSO-d₆): δ 2.23(s, 3H, CH₃), 1.80-2.46(m, 6H, 3 × CH₂), 4.60(s, 1H, CH), 5.45(s, 2H, NH₂), 7.29-7.60(m, 10H, Ar-H); ¹³C NMR: δ 21.00(CH₃), 21.20, 27.41, 36.40((-CH₂)₃), 28.32

Where
R₁ = H, 4-CH₃, 3-Cl
R₂ = H, CH₃
R₃ = H, CH₃, OCH₃, Cl, Br, NO₂

Scheme I
(-CH₃), 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-1H-pyrazol-4-yl)-1-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile D₁₅: IR (KBr): 3340-3315 (NH₂- stretching), 1988, 1662 cm⁻¹ (C=O-stretching); 1H NMR (DMSO-d₆): δ 2.20 (s, 3H, CH₃), 1.85-2.55 (m, 6H, 3 × CH₂), 4.65 (s, 1H, CH), 5.60 (s, 2H, NH₂), 7.45-8.38 (m, 9H, Ar-H); ¹³C NMR: δ 13.03(CH₃), 21.27, 27.66, 36.45(−CH₂), 28.82(−CH₃), 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-1H-pyrazol-4-yl)-1-(4-chlorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile D₁₆: IR (KBr): 3340-3320 (NH₂- stretching), 1901 (CN-stretching), 1655 cm⁻¹ (C=O-stretching); ¹H NMR (DMSO-d₆): δ 1.63 (s, 3H, CH₃), 2.19 (s, 3H, CH₃), 1.80-2.50 (m, 6H, 3 × CH₂), 4.62 (s, 1H, CH), 5.49 (s, 2H, NH₂), 7.31-7.62 (m, 8H, Ar-H); ¹³C NMR: δ 12.98, 21.09(−CH₃), 21.22, 27.50, 36.42(−CH₂), 28.37(−CH₂), 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-chlorophenyl)-3-methyl-1H-pyrazol-4-yl)-1-(4-methoxyphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile D₁₇: IR (KBr): 3442-3330 (NH₂- stretching), 2182 (CN-stretching), 1661 cm⁻¹ (C=O-stretching); ¹H NMR (DMSO-d₆): δ 2.17 (s, 3H, CH₃), δ 3.81 (s, 3H, OCH₃), 1.65-2.34 (m, 6H, 3 × CH₂), 4.64 (s, 1H, CH), 5.29 (s, 2H, NH₂), 7.10-7.65 (m, 8H, Ar-H); ¹³C NMR: δ 12.94(CH₃), 21.19, 27.54, 36.41(−CH₂), 28.31 (−CH₂), 55.96(OCH₃), 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-1H-pyrazol-4-yl)-1-(4-chlorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile D₁₈: IR (KBr): 3442-3330 (NH₂- stretching), 2182 (CN-stretching), 1661 cm⁻¹ (C=O-stretching); ¹H NMR (DMSO-d₆): δ 0.80 (s, 3H, CH₃), 0.86 (s, 3H, CH₃), 1.63 (s, 3H, CH₃), 1.74-2.36 (m, 4H, 2 × CH₂), 2.15 (s, 3H, CH₃), 4.62 (s, 1H, CH), 5.30 (s, 2H, NH₂), 7.10-7.63 (m, 8H, Ar-H); ¹³C NMR: δ 12.94, 20.60(−CH₂), 26.17, 27.50(−CH₂), 32.37(−CH₂), 36.94, 40.62 (−CH₂), 29.60(−CH₂), 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⁺).

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