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Synthesis of Some New Hydroquinoline and Pyrimido[4,5-b]Quinoline Derivatives

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ABSTRACT

A new series of hydroquinolines derivatives (1, 2) have been achieved by the cyclo condensation of 2 (4-methoxybenzylidenemalonitrile), aniline and dimedone in the presence of piperidine. Cyclization of 5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-2-(phenylamino)quinoline-3-carbonitrile (2) sulphuric acid at room temperature afforded 7,8-dihydro-4-(4-methoxyphenyl)-7,7-dimethylquinolin-5(6H)-one[2,3-b]2,3-dihydroquinolin-4(1H)-one (3). Several substituted pyrimido[4,5-b]quinoline derivatives (4, 5, 6 and 7) were synthesized from 2-amino-1,4,5,6,7,8-hexahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-1-phenylquinoline-3-carbonitrile (1) via cyclization with thiourea, chloroacetyl chloride, phenyl isothiocyanate and formamide, respectively. The condensation of dimedone, with 4-methoxybenzylidene malononitrile in the presence of trimethylamine afforded 11-amino-3,4,8,9-tetrahydro-12-(4-methoxyphenyl)-3,3,8,8-tetramethyl-2H-chromeno[2,3-b]quinoline-1, 10(7H,12H)-dione (8) but in ammonium acetate afforded 7,8-dihydro-4-(4-methoxyphenyl)-7,7-dimethylquinolin-5(1H,4H,6H)-one[2,3-b]4-amino-7,8-dihydro-7,7-dimethylquinolin-5(6H)-one (9). The structures of the synthesized compounds were elucidated by elemental analyses and spectral data.

Key words: Dimedone, 4-methoxybenzylidene malononitrile, thiourea, phenylisothiocyanate

INTRODUCTION

Hydroquinoline derivatives are an important heterocyclic compounds to synthesis of organic and medicinal chemistry. Most of compounds contains on quinolone ring used as antimalarial (Trivedi *et al.*, 2008), antibacterials (Dlugosz and Dus, 1996), antifungals (El-Sayed *et al.*, 2002a), anticancer agents (El-Sayed *et al.*, 2002b) and anti-inflammatory activities (Gavrilov *et al.*, 1988; El-Sayed *et al.*, 2004). Additionally, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids, rubber chemicals and flavoring agents. (Trivedi *et al.*, 2008). Due to its importance as substructures in a wide range of natural and designed products, still great efforts continue to be directed to the development of new quinoline-based structures. The work presented herein was to synthesize pyrimidoquinoline and fused quinoline derivatives using hexahydroquinolinecarbonitriles as parent.

MATERIALS AND METHODS

General procedures: Melting points were determined on Electro thermal IA 9,100 series digital melting point apparatus in capillaries and are uncorrected. The IR spectra were obtained in the solid state as potassium bromide discs using a Perkin-Elmer model 1430 spectrometer. ¹H NMR spectra were recorded on a Varian/Gemini 400 MHz spectrometer in DMSO-d₆ as a solvent and

TMS as an internal standard (chemical shifts in δ , ppm). Mass spectra were measured on an instrument VG-7035 at 70 or 15 eV. Elemental analyses were performed at the Micro analytical Centre, Cairo University and Giza, Egypt.

2-amino-1,4,5,6,7,8-hexahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-1-phenylquinoline-3-carbonitrile (1). **5,6,7,8-Tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-2-(phenylamino)quinoline-3-carbonitrile (2):** A mixture of the dimedone (1.46 g, 10 mmol), 4-methoxybenzylidene malononitrile (10 mmol), and aniline (0.66 g, 10 mmol) in presence of piperidine in absolute ethanol (50 mL) was refluxed 6 h. The reaction mixture was cooled and the resulting precipitate was filtered, and recrystallization from ethanol to give compound 1 while compound 2 was obtained by removed the solvent under vacuum and recrystallization from DMF.

Compound 1: IR (cm^{-1}): IR. 3223 (NH_2), 3091(CH arom.), 2922, 2860 (CH aliph.), 1712, (C = O). $^1\text{H-NMR}$ (DMSO- d_6): 0.98-1.02 (2s, 6H, 2CH_3), 2.02-2.26 (s, 4H, 2CH_2), 3.73 (s, 3H, OCH_3), 4.12 (s, 1H, CH), 6.82 (d, 2H, Ar-H), 6.9 1(s, 2H, NH_2), 7.03 (d, 2H, Ar-H). 7.62-7.86 (m, 5H, Ar-H). Anal. Calcd. For ($\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_2$, 399.48): C, 75.16; H, 6.31; N, 10.52. Found: C, 74.98; H, 6.02; N, 10.33.

Compound 2: IR (cm^{-1}): 3320 (NH), 3064 (CH arom.), 2924, 2870 (CH aliph.), 2197(CN), 1678, (C = O). $^1\text{H-NMR}$ (DMSO- d_6): 1.11-1.02 (2s, 6H, 2CH_3), 2.32-2.56 (s, 4H, 2CH_2), 3.73(s, 3H, OCH_3), 6.83 (d, 2H, Ar-H), 8.02 (s, 1H, NH), 7.33 (d, 2H, Ar-H). 6.62-7.06 (m, 5H, Ar-H). Anal. Calcd. For ($\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_2$, 397.47): C, 75.54; H, 5.83; N, 10.57. Found: C, 75.31; H, 5.93; N, 10.34.

7,8-dihydro-4-(4-methoxyphenyl)-7,7-dimethylquinolin-5(6H)-one[2,3-b]2,3-dihydroquinolin-4(1H)-one (3): A mixture of compound 2 (0.001 mol) in conc. H_2SO_4 (10 mL) and xylene was stirred for 8 h at room temperature, then the reaction mixture was evaporated. The obtained solid was washed with water and recrystallized from ethanol to give 3. IR (cm^{-1}): 3359 (NH), 3072 (CH arom.), 2918, 2873 (CH aliph.), 1708, (C = O), 1627 (C = N). $^1\text{H-NMR}$ (DMSO- d_6): 1.00, 1.04 (2s, 6H, 2CH_3), 1.99-2.14 (s, 4H, 2CH_2), 8.39(s, 1H, NH), 6.82 – 6.86 (d, 2H, Ar-H), 7.03-7.06 (d, 2H, Ar-H). 6.65-7.56(m, 4H, Ar-H). Anal. Calcd. For ($\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_3$, 398.45): C, 75.36; H, 5.57; N, 7.03. Found: C, 75.47; H, 5.67; N, 7.18.

4-amino-1,2,8,9-tetrahydro-5-(4-methoxyphenyl)-8,8-dimethyl-10-phenyl-2-thioxopyrimido[4,5-b]quinolin-6(5H,7H,10H)-one (4): A mixture of 1 (0.005 mol) and thiourea (0.005 mol) in absolute ethanol ml containing drops of hydrochloric acid (0.005 mol) was refluxed for 8 h. The reaction mixture was left to cool to room temperature, and then poured into ice cold water (50 mL) the separated material was filtered off and recrystallized from ethanol to give compounds 4. IR (cm^{-1}): 3390, 3359, 3263 (NH, NH_2), 3072 (CH arom.), 2960, 2885 (CH aliph.), 1708, (C = O), 1627 (C = N), 1337 (C = S). $^1\text{H-NMR}$ (DMSO- d_6): 1.00, 1.04 (2s, 6H, 2CH_3), 1.99-2.14 (s, 4H, 2CH_2), 4.75 (s, 1H, CH), 11.39 (s, 1H, NH), 9.20 (s, 1H, NH), 6.45 (s, 2H, NH_2), 6.82 – 6.86 (d, 2H, Ar-H), 7.03-7.06 (d, 2H, Ar-H). 7.12-7.56 (m, 5H, Ar-H). Anal. Calcd. For ($\text{C}_{26}\text{H}_{26}\text{N}_4\text{O}_2\text{S}$, 458.58): C, 68.10; H, 5.71; N, 12.22; S, 6.99. Found: C, 67.99; H, 5.98; N, 12.04; S, 6.74.

2-(Chloromethyl)-8,9-dihydro-5-(4-methoxyphenyl)-8,8-dimethyl-10-phenylpyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (5): A solution of 1 (0.001 mol) and chloroacetyl chloride

(1.12 g, 0.01 mol) in dimethyl formamide (20 mL) was refluxed for 12 h. The reaction mixture was cooled and then poured onto cold water and the residue was filtrated and recrystallized from dioxane to give 5. IR (cm^{-1}): 3233 (NH), 3072 (CH arom.), 2960, 2875 (CH aliph.), 1721, (C = O), 1623 (C = N), $^1\text{H-NMR}$ (DMSO- d_6): 1.03-1.07 (2s, 6H, 2 CH_3), 2.07-2.65 (2s, 4H, 2 CH_2), 4.82 (s, 1H, CH), 3.75 (s, 1H, OCH_3), 6.82-6.86 (d, 2H, Ar-H), 4.32 (s, 2H, CH_2), 7.03-7.06 (d, 2H, Ar-H), 7.34 (s, 1H, NH). Anal. Calcd. For $\text{C}_{27}\text{H}_{26}\text{ClN}_3\text{O}_3$, 475.97): C, 68.13; H, 5.51; Cl, 7.45; N, 8.83. Found: C, 68.24; H, 5.61; Cl, 7.75; N, 8.74.

1,2,3,4,8,9-hexahydro-4-imino-5-(4-methoxyphenyl)-8,8-dimethyl-3,10-diphenyl-2-thioxopyrimido[4,5-b]quinolin-6(5H,7H,10H)-one (6): A mixture of 1 (4.98 g, 0.01 mol), phenyl isothiocyanate (1.35 g, 0.01 mol) in pyridine (20 mL) was refluxed for 12 h and then the reaction mixture left to cool at room temperature. The reaction mixture was poured into cold water for complete precipitation, then filtered off washed with water dried well and recrystallized from dioxane to yield compounds 6. (265 mg, 64%), mp. 256-258°C. IR (cm^{-1}): 3263 (NH_2), 3153 (CH arom.), 2968, 2895 (CH aliph.), 1721, (C = O), 1636 (C = N), $^1\text{H-NMR}$ (DMSO- d_6): 1.03-1.07 (2s, 6H, 2 CH_3), 2.07-2.65 (2s, 4H, 2 CH_2), 4.82 (s, 1H, CH), 3.75 (s, 1H, OCH_3), 6.82-6.86 (d, 2H, Ar-H), 5.72 (s, 2H, 2NH), 7.03-7.06 (d, 2H, Ar-H). Anal. Calcd. For ($\text{C}_{32}\text{H}_{30}\text{N}_4\text{O}_2\text{S}$, 534.67): C, 71.88; H, 5.66; N, 10.48; S, 6.00. Found: C, 71.76; H, 5.43; N, 10.36; S, 6.13.

4-amino-8,9-dihydro-5-(4-methoxyphenyl)-8,8-dimethyl-10-phenylpyrimido[4,5-b]quinolin-6(5H,7H,10H)-one (7): A mixture of compound 1 (0.001 mol) and formamide (30 mL) was refluxed for 6 h. The reaction mixture was cooled and then poured onto ice-cold water, and the residue was filtrated and recrystallized from dioxane to 7. IR (cm^{-1}): 3225 (NH_2), 3072 (CH arom.), 2960, 2875 (CH aliph.), 1711, (C = O), 1632 (C = N), $^1\text{H-NMR}$ (DMSO- d_6): 1.03-1.07 (2s, 6H, 2 CH_3), 2.07-2.65 (2s, 4H, 2 CH_2), 4.82 (s, 1H, CH), 3.75 (s, 1H, OCH_3), 6.82-6.86 (d, 2H, Ar-H), 6.72 (s, 2H, NH_2), 7.03-7.06 (d, 2H, Ar-H), 7.34 (s, 1H, CH). Anal. Calcd. For ($\text{C}_{26}\text{H}_{26}\text{N}_4\text{O}_2$, 426.51): C, 73.22; H, 6.14; N, 13.14. Found: C, 73.31; H, 5.97; N, 12.96.

11-amino-3,4,8,9-tetrahydro-12-(4-methoxyphenyl)-3,3,8,8-tetramethyl-2H-chromeno[2,3-b]quinoline-1,10(7H,12H)-dione (8): A mixture of dimedone and 4-methoxybenzylidene malononitrile in presence of a catalytic amount of triethylamine (TEA), the reaction mixture was refluxed for 6 h, then the residue was filtered after cooling and recrystallized from ethanol to give 8 as white crystals. (285 mg, 67%), mp. 216-218 °C. IR (cm^{-1}): 3234 (NH_2), 3063 (CH arom.), 2960, 2875 (CH aliph.), 1713, (C = O), 1625 (C = N), $^1\text{H-NMR}$ (DMSO- d_6): 1.02-1.06 (s, 12H, 4 CH_3), 2.07-2.65 (4s, 8H, 4 CH_2), 4.74 (s, 1H, CH), 3.73(s, 1H, OCH_3), 6.82-6.86 (d, 2H, Ar-H), 6.93 (s, 2H, NH_2), 7.03-7.06 (d, 2H, Ar-H). Anal. Calcd. For $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_4$, 446.54): C, 72.62; H, 6.77; N, 6.27. Found: C, 72.73; H, 6.65; N, 6.32.

7,8-dihydro-4-(4-methoxyphenyl)-7,7-dimethylquinolin-5(1H,4H,6H)-one[2,3-b]4-amino-7,8-dihydro-7,7-dimethylquinolin-5(6H)-one (9): Treatment of dimedone with 4-methoxybenzylidene malononitrile in presence of ammonium acetate and glacial acetic acid the reaction mixture was refluxed for 14 h, then the reaction mixture was allowed to cool and the solid product was filtered, washed with water and recrystallized from dimethyl formamide to give 9. (265 mg, 75%), mp. 223-225°C. IR (cm^{-1}): 3359, 3263 (NH, NH_2), 3072 (CH arom.), 2950, 2835 (CH aliph.), 1716, (C = O), 1634 (C = N), $^1\text{H-NMR}$ (DMSO- d_6): 0.94-1.03 (s, 12H, 4 CH_3), 2.07-2.66

(4s, 8H, 4CH₂), 4.74 (s, 1H, CH), 3.37 (s, 1H, OCH₃), 6.82-6.86 (d, 2H, Ar-H), 6.91 (s, 2H, NH₂), 7.03-7.06 (d, 2H, Ar-H), 7.93 (s, 1H, NH). Anal. Calcd. For (C₂₇H₃₁N₃O₃, 445.55): C, 72.78; H, 7.01; N, 9.43. Found: C, 72.67; H, 6.96; N, 9.52.

RESULTS AND DISCUSSION

1, 4-dihydropyridines have received large attention because of their fundamental role in different biological processes. It has been reported many derivatives of dihydropyridines have been reported to have wide biological activity, e.g. it is used in the treatment of cardiovascular disease (calcium antagonist) (Goldmann and Stoltefuss, 1991; Litvinov, 1998). One agents cardiovascular known of this type is nifedipine (Balalaie *et al.*, 2008) synthesize novel 4H-benzo[b]pyrans via one-pot, three-component Tandem Knoevenagel cyclo condensation reaction, consisting of aromatic aldehyde, malononitrile and barbituric/thiobarbituric acid in aqueous ethanol at room temperature. It should be noted here that when aniline was reacted with 2 (4-methoxybenzylidenemalonitrile) and dimedone, in the presence of a catalytic amounts of piperidine, afforded two products were isolated; one is the expected hexahydroquinoline derivative 1 and the other is the unexpected 5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-2-(phenylamino)quinoline-3-carbonitrile 2, where, the major product is the hexahydroquinoline derivative 1 (Fig. 1).

When 5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-2-(phenylamino)quinoline-3-carbonitrile 2 was stirring with concentrated sulphuric acid at room temperature the cyano group was partially hydrolysis and elimination ammonia to afford compound 3 (Fig. 1).

Several cyclization reactions were reported for the synthesis of pyrimido[4,5-b]quinolone derivatives from 2-amino-1,4,5,6,7,8,-hexahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-1-phenylquinoline-3-carbonitrile 1. When compound 1 was refluxed with formamide to afford compound 7. The reaction proceeded via elimination a molecule of water, followed by intramolecular cyclization. The structure of 7 was confirmed by IR spectrum, which showed the absent of (CN) and the present of (NH₂) at 3225, (CH arom.) at 3072, (CH aliph.) at 2960 and (C = O) at 1711 cm⁻¹. The compound 1 was refluxed with chloroacetyl chloride in the presence of dimethyl formamide to afford 2-(chloromethyl)-8,9-dihydro-5-(4-methoxyphenyl)-8,8-dimethyl-10-phenylpyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione 5, where cyclization occurred through elimination a molecule of hydrogen chloride, followed by intramolecular cyclization and finally

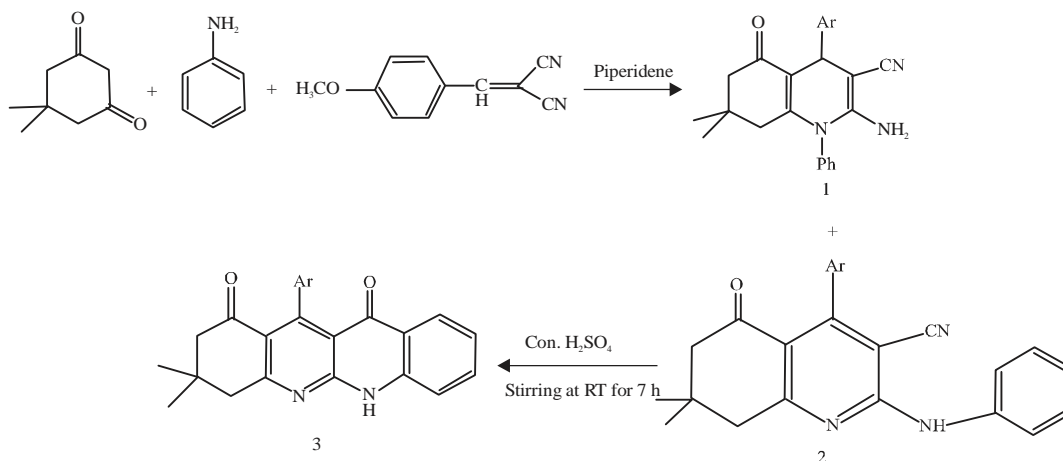


Fig. 1: Synthetic pathways for preparation of compounds 1-3

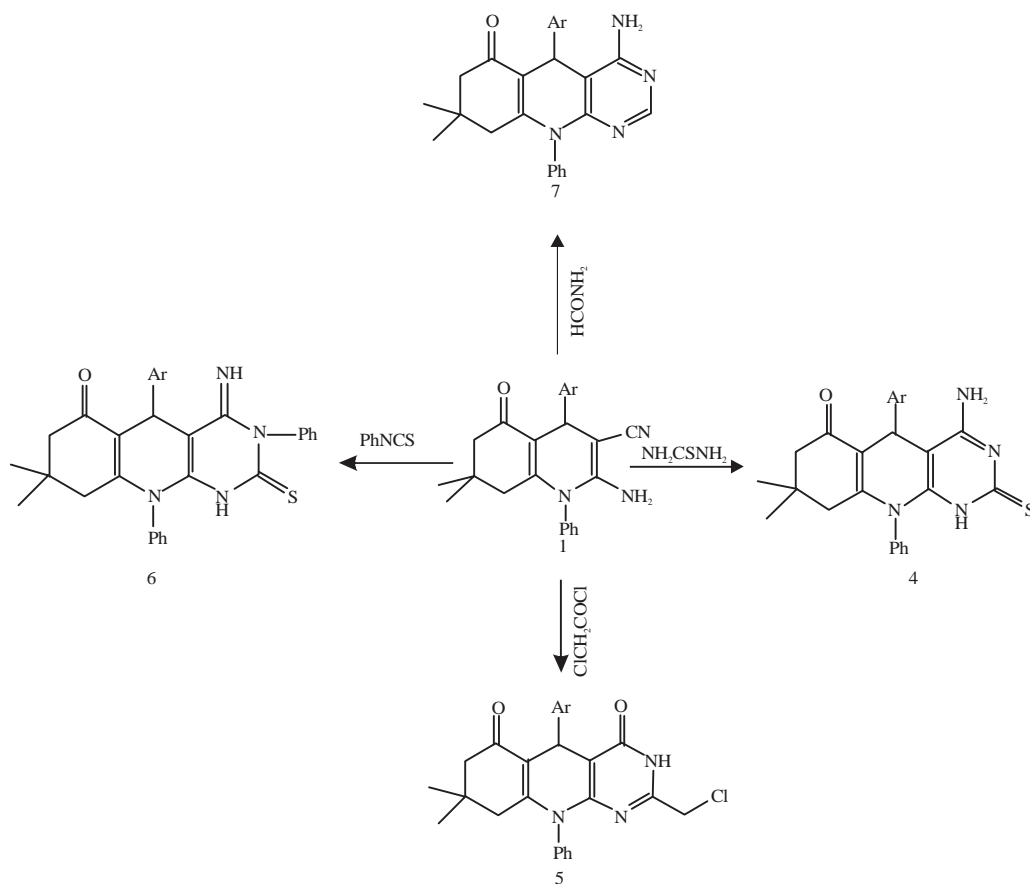


Fig. 2: Synthetic pathways for preparation of compounds 4-7

dimroth rearrangement. Compound 1 reacted with thiourea in presence of ethanol and drops of concentrated hydrochloric acid afforded compound 4. The reaction proceeded via elimination a molecule of ammonia, followed by addition to cyano group to yield the desired product 4. Pyrimido quinoline derivative 6 was synthesized by refluxed compound 1 with phenylisothiocyanate in pyridine (Fig. 2).

In order to study the generality of our methodology towards polycyclic compounds, the compound 8 was synthesized by the reaction of dimedone with 4-methoxybenzylidene malononitrile in the presence of triethylamine.

In another way, compound 9 was synthesized through the three substances condensation of dimedone, ammonium acetate used as the nitrogen source and 4-methoxybenzylidene malononitrile in the presence of acetic acid (Fig. 3).

A proposed mechanism for the synthesis of compound 9 is showed in Fig. 4. At first, a molecule of dimedone with ammonium acetate gives the enamine intermediate A which reacts with benzylidene malononitrile via Michael addition reaction to produce the adduct product B. Finally, after an intermediate molecular cyclization the compound B is converted to compound C which then, condensed with another molecule of dimedone and after an intramolecular cyclization followed by dehydration gives the compound 9 (Fig. 4).

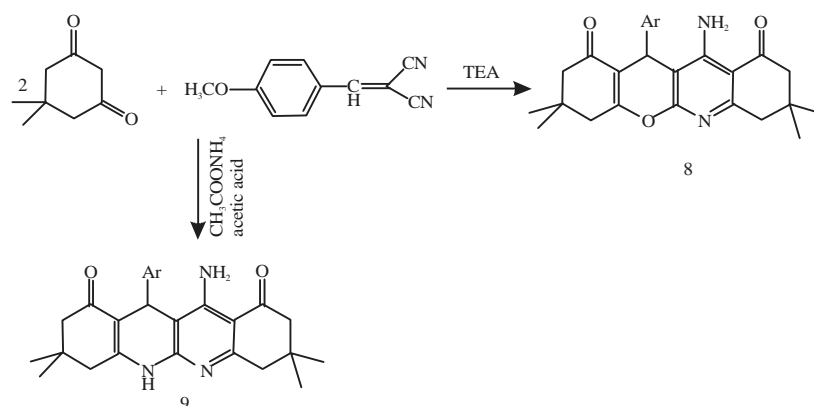


Fig. 3: Synthetic pathways for preparation of compounds 8, 9

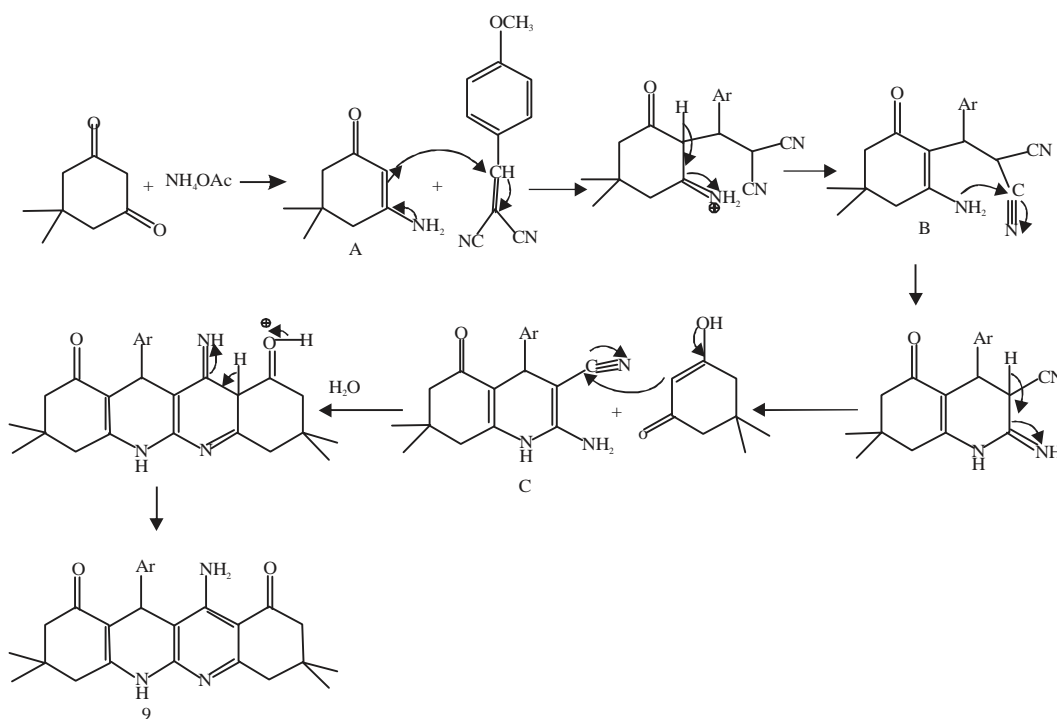


Fig. 4: Mechanism for the synthesis of compound 9

CONCLUSION

Thus, we have synthesized hydroquinolines and pyrimido[4,5-b]quinoline derivatives 4, 5, 6, 7, 8 and 9 were synthesized starting from 2-amino-1,4,5,6,7,8-hexahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-1-phenylquinoline-3-carbonitrile 1. The structures of the synthesized compounds were elucidated by elemental analyses and spectral data.

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