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POTENT ANTIMICROBIAL TETRAHYDROPYRIMIDOQUINOLINE DERIVATIVES

Sherif M. Sherif^{* 1} and Huda R. M. Rashdan²

Department of Chemistry¹, Faculty of Science, Cairo University, (Dean of Faculty of Science, Cairo University), Giza 12613, Egypt.

Department of Chemistry of Natural and Microbial Products², Pharmaceutical and Drug Industries Research Division, National Research Center, Giza, Egypt.

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Correspondence to Author:

Sherif M. Sherif

Department of Chemistry,
Faculty of Science, Cairo University,
Giza 12613, Egypt.

E-mail: hudadawoud20@yahoo.com

ABSTRACT: 2-Amino-1-aryl-1, 4, 5, 6, 7, 8-hexahydro-4-phenyl-quinoline-3-carbonitrile derivatives were synthesized by the reaction of cyclohexanone (1) with 2-benzylidene-malononitrile (2) and the appropriate of aniline derivatives. The reactivity of some of these newly synthesized derivatives toward carbon disulfide and further toward hydrazonoyl halides were also studied. Also, the antimicrobial activity of the newly synthesized derivatives was reported.

INTRODUCTION: The biological and pharmaceutical importance of pyrimidoquinoline derivatives stimulated the recent interest in the synthesis of these ring systems. This biological importance includes antimalarial¹, anticancer², antimicrobial^{3,4} and anti-inflammatory activities⁵.⁶ Recently, there has also been considerable interest in the synthesis of tetra hydroquinolines and their fused derivatives⁷⁻¹¹. The aim of the work presented herein was to synthesize pyrimido [4,5-*b*] quinolones using tetrahydro quinoline carbonitriles as building blocks. Such a synthesis of condensed azines is of biological interest due to the isoelectronic relationship that exists between the pyrimidine ring and tetrahydroquinoline¹²⁻²³.

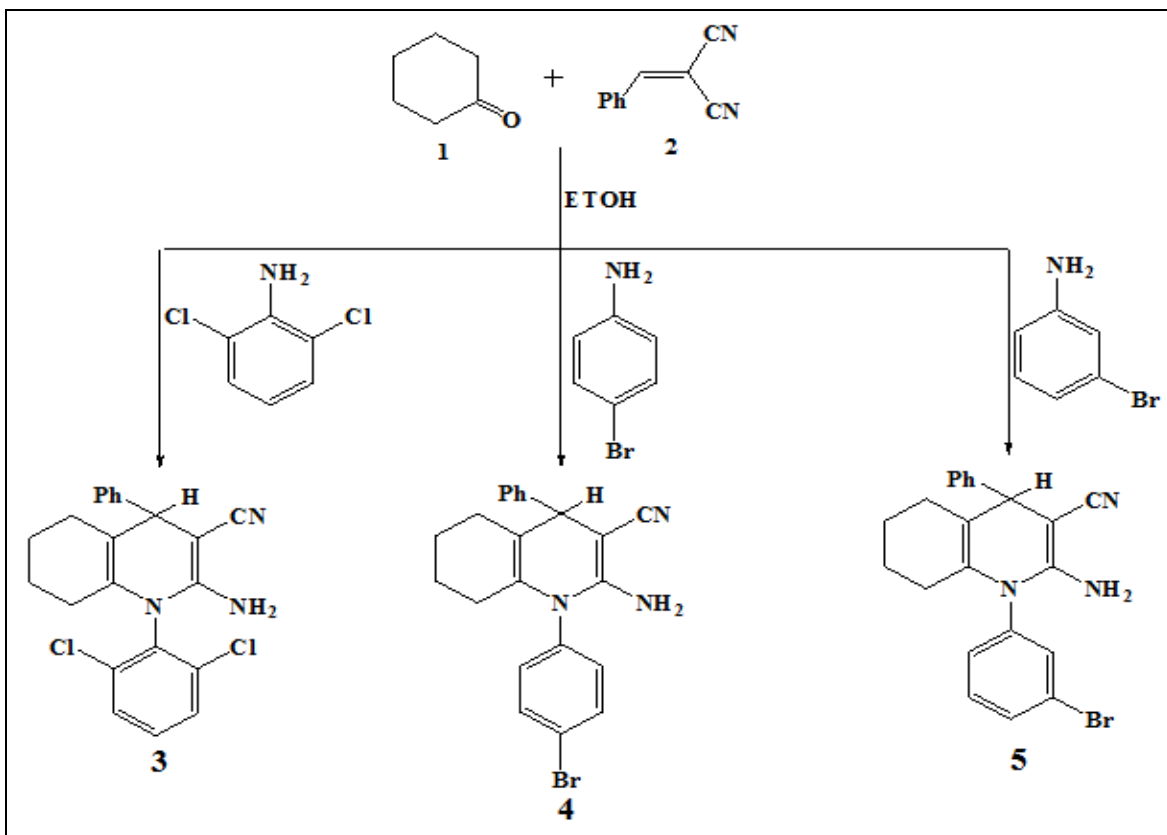
RESULT AND DISCUSSION: The reaction of cyclohexanone (1) with 2-benzylidene-malononitrile (2) and the appropriate of 4-fluoroaniline in ethanol (20) ml afforded 2-amino-1-(4-fluorophenyl)-1,4,5,6,7,8-hexahydro - 4 - phenyl-quinoline - 3 - carbonitrile (3) **Scheme 1**.

Compound 3 reacted with carbon disulfide to yield the target ring system 8 through the intermediates 6 and 7, whose subsequent rearrangement leads to the fused pyrimidinedione 8 **Scheme 2**.

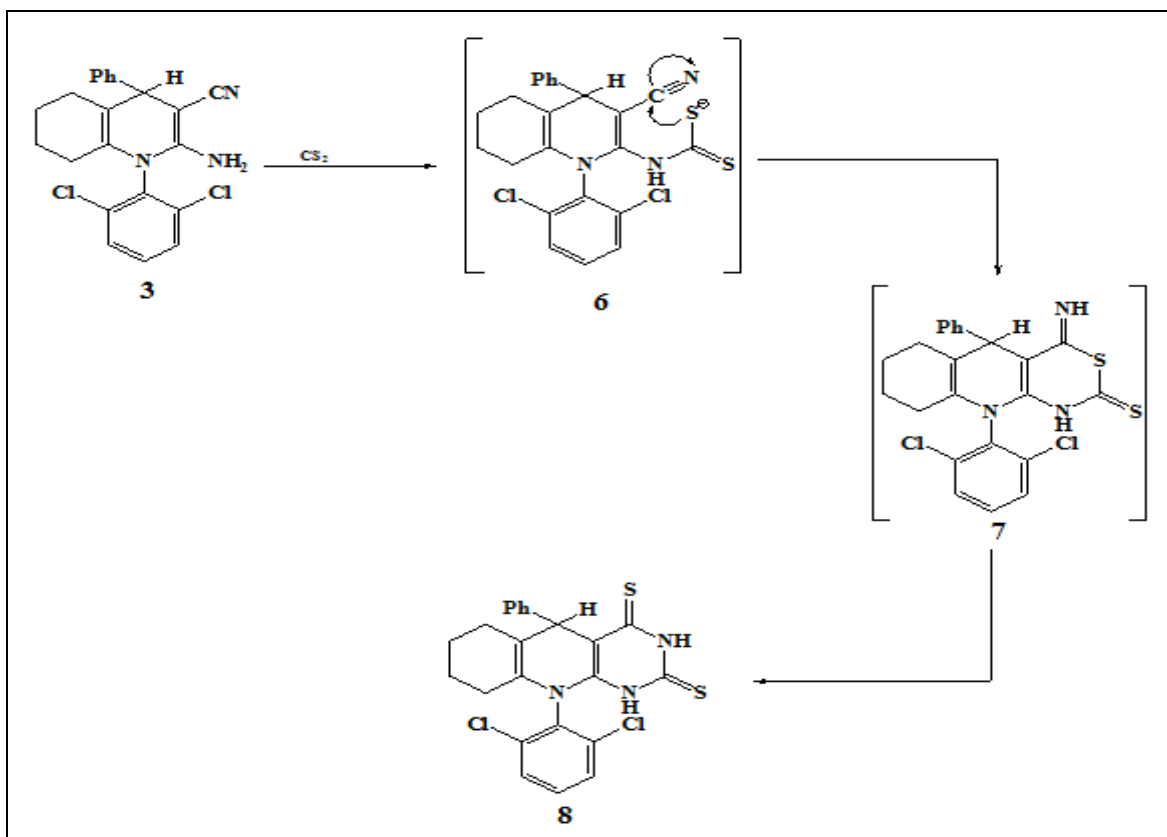
Compound 8 reacted with the appropriate of hydrazonoyl halides in chloroform in the presence of catalytic amount of triethylamine under reflux to give the corresponding derivatives 9a-c, 10 and 11a, b the structure of these compounds confirmed by elemental analysis, spectral data (IR, NMR, Mass) where, compound 9a showed IR signals at 1735(C=O), 2937, 2868(CH-aliphatic) and showed ¹H NMR signals at 1.22-2.89(m, 11H, 4CH₂, 3H-CH₂CH₃), 4.3-4.35(q, 2H, CH₂CH₃), 4.7(s, 1H, CH), 7.30-7.54(m, 13H, Ar-H).

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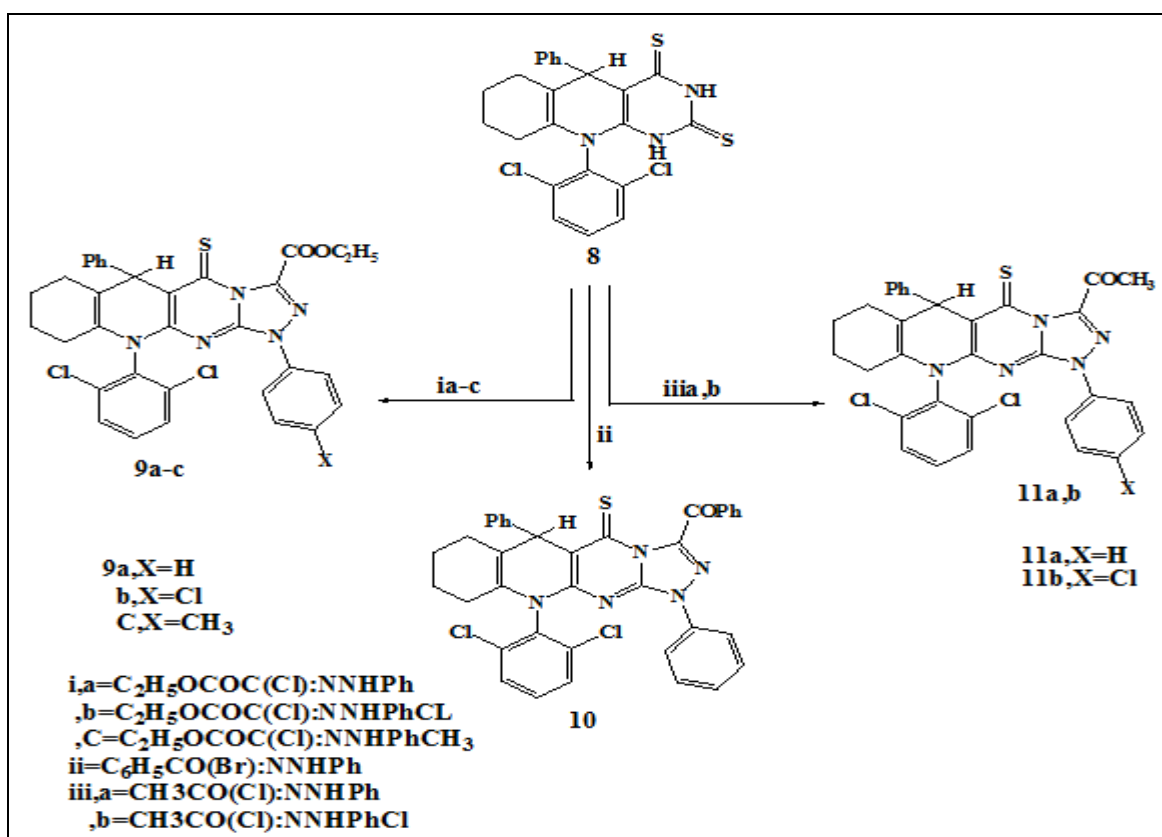
Also, compound 10 showed IR signals at 1680(C=O), 2936, 2871(CH-aliphatic) and H^1NMR signals at 1.40-2.81(m, 8H, 4CH₂), 4.67(s, 1H, CH), 7.13-7.59(m, 18H, Ar-H) **Scheme 3**.



SCHEME 1



SCHEME 2



SCHEME 3

Biological Activity: Screening of antimicrobial activity was performed at a Microbiology Lab in the Faculty of Agriculture, El-Azhar University, Cairo, Egypt. All the tested microorganisms were chosen on the bases of their pathogenicity. Where, *Aspergillus* caused a broad spectrum of disease in the human host, ranging from hypersensitivity reactions to direct angioinvasion. *Aspergillus* primarily affects the lungs, causing four main syndromes, including allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing *Aspergillus pneumonia* (or chronic necrotizing pulmonary aspergillosis [CNPA]), aspergilloma, and invasive aspergillosis. However, in patients who are severely immunocompromised, *Aspergillus* may hematogenously disseminate beyond the lung, potentially causing endophthalmitis, endocarditis, and abscesses in the myocardium, kidney, liver, spleen, soft tissue, and bone. On the other hand, *Candida albicans* is a diploid fungus that grows both as yeast and filamentous cells and a causal agent of opportunistic oral and genital infections in humans^{24, 25}.

C. albicans have emerged as important causes of morbidity and mortality in immunocompromised

patients (e.g., AIDS, cancer chemotherapy, organ or bone marrow transplantation). Also, *Staphylococcus aureus* can cause a range of illnesses, from minor skin infections, such as pimples, impetigo, boils (furuncles), cellulitis folliculitis, carbuncles, scalded skin syndrome, and abscesses, to life-threatening diseases such as pneumonia, meningitis, osteomyelitis, endocarditis, toxic shock syndrome (TSS), bacteremia, and sepsis. Its incidence ranges from the skin, soft tissue, respiratory, bone, joint, endovascular to wound infections.

It is still one of the five most common causes of nosocomial infections and is often the cause of postsurgical wound infections. Each year, some 500,000 patients in American hospitals contract a staphylococcal infection²⁶. Also, some *Bacillus* species can cause food poisoning; *Bacillus* can result in two different kinds of intoxications.

It can either cause nausea, vomiting, and abdominal cramps for 1-6 h, or diarrhea and abdominal cramps for 8-16 h. The food poisoning usually occurs from eating rice that is contaminated with *Bacillus subtilis* (EMBL EBI), Some *Bacillus* organisms can cause more severe illnesses, for

example, causes Anthrax. Also, *Salmonella typhimurium* is a pathogenic Gram-negative bacteria predominately found in the intestinal lumen. Its toxicity is due to an outer membrane consisting largely of lipopolysaccharides (LPS) which protect the bacteria from the environment.

Salmonella typhimurium causes gastroenteritis in humans and other mammals. And finally, pathogenic strains of *E. coli* are responsible for three types of infections in humans: urinary tract infections (UTI), neonatal meningitis, and intestinal diseases (gastroenteritis).

Representative derivatives 3, 4, 5, 8, 9a, 9b, 9c, 10, 11a and 11b were selected and tested for their antimicrobial activity against two gram(+) bacteria (*Staphylococcus aureus*, *Bacillus subtilis*), two gram(-) bacteria (*Escherichia coli*, *salmonella Typhimurium*) and a filamentous fungus (*Aspergillus fumigatus*) and a diploid fungus (*Candida albicans*). Using the modified Kirby-Bauer disc diffusion method^{27, 28, 29}. For the disc diffusion, the zone diameters were measured with slipping calipers of the national committee for clinical laboratory standards³⁰. The results are given in **Table 1**.

TABLE 1: RESPONSE OF VARIOUS MICROORGANISMS TO SOME SYNTHESIZED COMPOUNDS IN IN-VITRO CULTURE

Sample	Inhibition zone diameter (mm/mg sample)					
	Antimicrobial activity%					
	<i>A. fumigatus</i>	<i>C. albicans</i>	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>S. typhimurium</i>
DMSO (positive control)	0.00	0.00	0.00	0.00	0.00	0.00
Tetracycline (Antibacterial agent)	--	--	30	29	31	30
Clotrimazole (Antifungal agent)	24	22	--	--	--	--
3	22	16	23	22	24	27
	92%	73%	77%	76%	77%	90%
4	14	8	17	16	17	14
	58%	36%	57%	55%	55%	47%
5	16	7	15	10	12	15
	67%	32%	50%	34%	50%	50%
8	9	0.00	21	12	5	0.00
	38%	0.00	70%	41%	16%	0.00
9a	12	9	5	12	19	14
	50%	41%	17%	41%	61%	47
9b	19	18	9	23	25	23
	79%	82%	30%	79%	81%	77%
9c	15	5	3	14	11	10
	63%	23%	10%	48%	35%	33%
10	10	12	14	0.00	0.00	0.00
	42%	55%	47%	0.00	0.00	0.00
11a	4	0.00	12	14	14	12
	17%	0.00	40%	48%	45%	40%
11b	14	0.00	23	22	23	25
	58%	0.00	77%	76%	74%	83%

Antimicrobial activity % = Inhibition zone diameter of the tested sample × 100 / Inhibition zone diameter of the standard

Strong effect means: antimicrobial activity% ≥ 60%

Moderate effect means: 60% > antimicrobial activity% ≥ 40%

Weak effect means: 40% > antimicrobial activity% ≥ 1%

No effect means: antimicrobial activity%=0.00%

CONCLUSION: The varied biological activities of the newly synthesized compounds promoted us to synthesize some new derivatives of these ring systems and study their antimicrobial activities, their biological activities depended mainly on the nature and the position of the substituents. The antifungal activity studies revealed that compounds

3, 5, 9b and 9c show strong effects against *Aspergillus fumigatus*. Also, compounds 3 and 9b show strong effects against *Candida albicans*. On the other hand compounds 3, 8 and 11b display strong effects against *Staphylococcus aureus*. Compounds 3, 9b and 11b give strong effects against *Bacillus subtilis*. Compounds 3, 9a, 9b and

11b show strong effects against *Escherichia coli*. And finally compounds 3, 9b and 11b afford strong effects against *Salmonella Typhimurium*. All the other compounds show effects against different types of tested microorganisms ranged from negative effects to moderate effects.

So we can say that the synthesis of new derivatives of these compounds is still an active area of research. Where synthesis and study of the antimicrobial activities of new analogous of these compounds will be helpful for a medicinal chemist to focus design of novel chemical entities containing pyrimidoquinoline derivatives as a part of antimicrobial drugs.

Experimental:

Experimental Instrumentation: All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on Shimadzu FT-IR 8201 PC spectrophotometer. ^1H NMR and spectra were recorded in CDCl_3 and $(\text{CD}_3)_2\text{SO}$ solutions on a Varian Gemini 300 MHz FT-NMR system spectrometer and chemical shifts are expected in δ ppm units using TMS as an initial reference. Mass spectra were recorded on GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of Cairo University. Hydrazonoyl halides ^{31, 32} were prepared as previously reported.

Synthesis:

2-amino-1 - (4 - fluorophenyl) - 1, 4, 5, 6, 7, 8-hexahydro-4-phenylquinoline-3-carbonitrile (3): A mixture of cyclohexanone (1) (1 ml, 10 mmol), 2-benzylidinemalononitrile (2) (1.5 gm, 10 mmol) and 2,6-dichloroaniline (1.6 gm, 10 mmol) in absolute ethanol (20 ml) was heated under reflux for 10-12 h. Then the reaction mixture left to cool to room temperature overnight. The solid obtained was recrystallized from ethanol to afford the corresponding compound 3 in a good yield. Yield: 84%; MP: 230-232 °C; FT-IR: 3419, 3340(NH_2), 2933, 2864(CH-aliphatic), 2210(CN), 1647(C=C); ^1H NMR (300MHz, DMSO-*d*6): 1.64-2.77(m, 8H, 4 CH_2), 4.5(s, 1H, CH), 5.7(s, 2H, NH_2), 7.1-7.4(m, 8H, Ar-H); MS (El, m/z (%)): 397(M+2, 97%), 396(M+1, 15%), 395(M^+ , 100%); Anal. Calcd. For $\text{C}_{22}\text{H}_{19}\text{Cl}_2\text{N}_3$ (395): C, 66.67; H, 4.83; N, 10.60 Found: C, 66.68; H, 4.83; N, 10.61%.

2-amino - 1 - (4-bromophenyl) - 1, 4, 5, 6, 7, 8 - hexahydro-4-phenylquinoline-3-carbonitrile (4): A mixture of cyclohexanone (1) (1ml, 10 mmol), 2-benzylidinemalononitrile (2) (1,5gm, 10 mmol) and 4-bromoaniline (1.7 gm, 10 mmol) in absolute ethanol (20 ml) was heated under reflux for 10-12 hrs. Then the reaction mixture left to cool to room temperature overnight. The solid obtained was recrystallized from ethanol to afford the corresponding compound 3 in a good yield. Yield: 81%; MP: 275-277 °C; FT-IR: 3417, 3339(NH_2), 2932, 2864(CH-aliphatic), 2209(CN), 1647(C=C); ^1H NMR: 1.45-2.8(m, 8H, 4 CH_2), 4.5(s, 1H, CH), 5.74(s, 2H, NH_2), 7.3-7.5(m, 9H, Ar-H); (300MHz, DMSO-*d*6): MS (El, m/z(%)): (M+2, 92%), (M+1, 4%), (M^+ , 100%); Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{BrN}_3$ (405): C, 65.03 ; H, 4.96 4.29; N, 10.34 Found: C, 61.82; H, 4.28; N, 18.80%.

2-amino- 1 - (3-bromophenyl) - 1, 4, 5, 6, 7, 8 - hexahydro-4-phenylquinoline-3-carbonitrile (5): A mixture of cyclohexanone (1) (1 ml, 10 mmol), 2-benzylidinemalononitrile (2) (1.5 gm, 10 mmol) and 3-bromoaniline (1.7 gm, 10 mmol) in absolute ethanol (20 ml) was heated under reflux for 10-12 hrs. Then the reaction mixture left to cool to room temperature overnight. The solid obtained was recrystallized from ethanol to afford the corresponding compound 3 in a good yield. Yield: 78%; MP: 286-288 °C; FT-IR: 3418, 3339(NH_2), 2931, 2864(CH-aliphatic), 2212(CN), 1647(C=N); ^1H NMR: 1.45-2.8(m, 8H, 4 CH_2), 4.5(s, 1H, CH), 5.72(s, 2H, NH_2), 7.3-7.54(m, 9H, Ar-H); (300MHz, DMSO-*d*6): MS (El, m/z(%)): 407(M+2, 32%), 406(M+1, 45%), 405(M^+ , 34%); Anal. Calcd. $\text{C}_{22}\text{H}_{20}\text{BrN}_3$ (405): C, 65.03; H, 4.96 4.29; N, 10.34 Found: C, 61.82; H, 4.28; N, 18.80%.

10 - (2,6-dichlorophenyl)-6, 7, 8, 9- tetrahydro-5-phenylpyrimido[4,5-b]quinoline-2,4(1H, 3H, 5H, 10H)-dithione (8): To a solution of 3(2 gm, 5 mmol) in dry pyridine (30 ml) carbon disulfide (5 mmol) was added and the reaction mixture was refluxed on water bath for 6 h then left to cool to room temperature, poured onto ice-cold water and neutralized with diluted hydrochloric acid to complete precipitation. The solid obtained was filtered off, washed, dried well and recrystallized from methanol to give 8 as orange crystals. Yield: 78%; MP: 207-209 °C; FT-IR: 3300(NH), 2831, 2764(CH-aliphatic); ^1H NMR: 1.45-2.8(m, 8H,

4CH₂), 4.5(s, 1H, CH), 7.32-7.54(m, 8H, Ar-H), 11.0(s, 2H, NH); (300MHz, DMSO-*d*₆): MS (EI, m/z(%)): 473(M+2, 98%), 472(M+1, 21%), 471(M⁺, 100%); Anal. Calcd. C₂₃H₁₉Cl₂N₃S (471): C, 58.47; H, 4.05; N, 8.89 Found: C, 58.46; H, 4.03; N, 8.88%.

General method for the synthesis of 9a-c, 10, 11a and 11b: A mixture of 8(4.7 gm, 10 mmol) and the appropriate of hydrazonoylhalides (10 mmol) was boiled under reflux in chloroform (30 ml) containing a catalytic amount of triethylamine (10 drops) for 12-15 h. The reaction mixture was left overnight for cooling, the solid collected and recrystallized from the proper solvent to give the corresponding 9a-c, 10, 11a and 11b respectively.

Ethyl (6, 10-diphenyl- 1 - (2, 6-dichlorophenyl)-7-thio-1, 2, 3, 4, 5, 6-hexahydro - 1, 7a, 9, 10, 11-pentaazacyclopenta[a]anthracene) acetate (9a): Yellow crystals from ethanol. Yield: 72%; MP: 194-196 °C ; FT-IR: 1735(C=O), 2937, 2868(CH-aliphatic); H¹NMR: 1.22-2.89(m, 11H, 4CH₂, 3H-CH₂CH₃), 4.3-4.35(q, 2H, CH₂CH₃), 4.7(s, 1H, CH), 7.30-7.54(m, 13H, Ar-H); (300MHz, DMSO-*d*₆): MS (EI, m/z(%)): 629(M+2, 73%), 628(M+1, 34%), 627(M⁺, 70%); Anal. Calcd. C₃₃H₂₇Cl₂N₅O₂S (627): C, 63.06; H, 4.33; N, 11.14 Found: C, 63.06; H, 4.33; N, 11.12%.

Ethyl (6-phenyl – 10 - (p-chlorophenyl)-1-(2, 6 - dichlorophenyl)-7- thio- 1,2,3,4,5,6-hexahydro-1, 7a, 9,10,11-pentaazacyclopenta [a] anthracene) acetate(9b): Yellow crystals from ethanol. Yield: 74%; MP: 187-189 °C; FT-IR: 1739(C=O), 2939, 2878(CH-aliphatic); H¹NMR: 1.20-2.87(m, 11H, 4CH₂, 3H-CH₂CH₃), 4.31-4.35(q, 2H, CH₂CH₃), 4.7(s, 1H, CH), 7.33-7.52(m, 12H, Ar-H); (300MHz, DMSO-*d*₆): MS (EI, m/z(%)): 665(M+2, 3%), 664(M+1, 70%), 663(M⁺, 4%); Anal. Calcd. C₃₃H₂₆Cl₃N₅O₂S (663): C, 59.78; H, 3.95; N, 10.56 Found: C, 59.78; H, 3.95; N, 10.56%.

Ethyl (6-phenyl - 10 - (p-methylphenyl) – 1 - (2, 6 - dichlorophenyl)-7-thio-1,2,3,4,5,6-hexahydro-1,7a,9,10,11-pentaazacyclopenta [a] anthracene) acetate(9c): Yellow crystals from ethanol. Yield: 71%; MP: 190-192 °C; FT-IR: 1737(C=O), 2939, 2878(CH-aliphatic); H¹NMR: 1.20-2.87(m, 14H, 4CH₂, 3H-CH₃, 3H-CH₂CH₃), 4.31-4.35(q, 2H, CH₂CH₃), 4.7(s, 1H, CH), 7.33-7.54(m, 12H, Ar-

H); (300MHz, DMSO-*d*₆): MS (EI, m/z(%)): 643(M+2, 81%), 642(M+1, 27%), 641(M⁺, 80%); Anal. Calcd. C₃₄H₂₉Cl₂N₅O₂S (641): C, 63.55; H, 4.55; N, 10.90 Found: C, 63.53; H, 4.55; N, 10.89%.

6,10-diphenyl -8-benzoyl-1-(2,6-dichlorophenyl)-7-thio-1, 2, 3, 4 ,5, 6- hexaahydro - 1, 7a, 9, 10, 11-pentaazacyclopenta[a]anthracene(10): Pale yellow crystals from ethanol. Yield: 79%; MP: 150-152 °C; FT-IR: 1680(C=O), 2936, 2871(CH-aliphatic); H¹NMR: 1.40-2.81(m, 8H, 4CH₂), 4.67(s, 1H, CH), 7.13-7.59(m, 18H, Ar-H); (300MHz, DMSO-*d*₆): MS (EI, m/z(%)): 661(M+2, 14%), 660(M+1, 27%), 659(M⁺, 13%); Anal. Calcd. C₃₇H₂₇Cl₂N₅OS (659): C, 67.27; H, 4.12; N, 10.60 Found: C, 67.27; H, 4.12; N, 10.61%.

6, 10-diphenyl-8-acetyl-1-(2, 6-dichlorophenyl)-7-thio-1,2,3,4,5,6-hexaahydro-1,7a,9,10,11-penta azacyclopenta [a] anthracene (11a): Yellow crystals from ethanol. Yield: 73%; MP: 163-165 °C; FT-IR: 1690(C=O), 2935, 2879(CH-aliphatic); H¹NMR: 1.43-2.89(m, 11H, 4CH₂, 3H-CH₃), 4.7(s, 1H, CH), 7.33-7.54(m, 13H, Ar-H); (300MHz, DMSO-*d*₆): MS (EI, m/z(%)): 600(M+2, 9%), 599(M+1, 12%), 598(M⁺, 11%); Anal. Calcd. C₃₂H₂₅Cl₂N₅OS (598): C, 64.21; H, 4.21; N, 11.70 Found: C, 64.21; H, 4.22; N, 11.68%.

6-phenyl- 10 - (p-chlorophenyl) - 8 - acetyl - 1 - (2, 6-dichlorophenyl)-7-thio-1, 2, 3,4,5,6-hexahydro-1, 7a, 9, 10, 11-pentaazacyclopenta[a]anthracene (11b): Yellow crystals from ethanol. Yield: 75%; MP: 171-173 °C; FT-IR: 1689(C=O), 2935, 2883(CH-aliphatic); H¹NMR: 1.42-2.88(m, 11H, 4CH₂, 3H-CH₃), 4.7(s, 1H, CH), 7.33-7.54(m, 12H, Ar-H); (300MHz, DMSO-*d*₆): MS (EI, m/z(%)): 633(M+2, 75%), 632(M+1, 6%), 631(M⁺, 80%); Anal. Calcd. C₃₂H₂₄Cl₃N₅OS (631): C, 60.72; H, 3.82; N, 11.06 Found: C, 60.71; H, 3.81; N, 11.04%.

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