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Synthesis, Characterization and Biological Activities of Pyrimido and Mercaptopyrimidocycloocta[*b*]indole Derivatives.

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ABSTRACT

A resourceful method for the synthesis and study of biological activity of eight membered indole fused compounds analog to pyrimidine derivatives of natural product. With the precursor cycloocta[*b*]indole, which was prepared by the reported method, 4-methyl-benzaldehyde is supposed to condense and to give condensed product namely, 2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole **(3).** Further compounds were prepared namely, pyrimidocycloocta[*b*]indole and merceptopyrimidocycloocta[*b*]indole derivatives by allowing the appropriate condensed product to react with urea and thiourea, which results in the formation of 2-hydroxy-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indoles **(4)** and 2-mercapto-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indoles **(5)** respectively. Biological activities for the synthesized compounds were studied against bacterial and fungal strains which show moderate potency of the prepared compounds.

Keywords: cycloocta[*b*]indole, methyl-benzaldehyde, mercaptopyrimido, pyrimido, thiourea, urea.

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INTRODUCTION

Related to alkaloids or terpenoids, hetero atom containing ring systems are normally grouped on the basis of the annulations and substitutions present in them. Some common ring systems, including indolizidine- and quinolizidine- based systems [1] and quinoline- and quinazoline- based systems [2] were evaluated recently, including their biosynthesis [3]. Many of the alkaloids are directly derived from the aromatic amino acids, phenylalanine, etc. Notable indole alkaloids are reserpine, an antihypertensive alkaloid from Indian snakeroot (*Rauwolfia serpentina*), and vinblastine, one of the antitumor alkaloids, from the rosy periwinkle (*Catharanthus roseus*). People have been using alkaloids in the form of plant extracts for several thousand years. Thus, many of the common drugs used (and abused) today are alkaloid based. Common examples include caffeine, quinine, and nicotine. More potent examples include cocaine, morphine, and strychnine. Alkaloids in plants serve as chemoprotective antiherbivory agents or as growth regulators, such as the well-known plant hormone, indole-3-acetic acid, IAA (an indole derivative synthesized from tryptophan — see Buchanan et al., 2000).

For some indoles it is necessary to control regioselectivity with unsymmetrical carbonyl compounds. Ondansetron, an anti-nausea compound that is used to help cancer patients take larger doses of antitumour compounds than was previously possible, is an example. It contains indole and imidazole ring. Usually make the rings by cyclization reactions with the heteroatom (O, N, S) as a nucleophile and a suitably functionalized carbon atom as the electrophile. This electrophile will almost always be a carbonyl compound. A potent central nervous system stimulant is strychnine. As Nitrogen containing heterocycles, are presenting broad pharmaceutical interest [4-5] that justifies the continuing efforts in the development of structure activity relationship of novel compounds in this series of new synthetic strategies.

Analog to purine or pyrimidine bases are more attractive for the research activities which are promising for their potency in the biological and organic fields. It is intended to adventure about the indole and pyrimidine containing or fused compounds with the structural coincidence in the classification of alkaloids [6] or terpenoids. More structure-based natural products research has began around 150 years ago, focused on the alkaloids, or “vegetable alkalis,” as they were known. They are highly varied and often complex three-dimensional chemical structures. The content of this report is about Pyrimido and Mercapto-pyrimido compounds of cyclooct[*b*]indole derivatives with simple strategies of preparation and characterization which plunge into identify their structure and activities.

MATERIALS AND METHODS

All the chemicals and reagents were bought from himedia and rankem companies, India Pvt. Ltd., except cyclooctanone and 4-methyl-benzaldehyde which were supplied by Sigma Aldrich Chemical Co., USA. (A.R grade) Preparations were done by the appropriate procedure as in the experimental section and they are purified for the further reactions, analyses and application studies. Purification is done by using petroleum ether and ethyl acetate as eluent.

Melting point of all compounds was noted through Raaga Melting point apparatus. The elemental analysis of the compounds were done using Elementar Vario EL III analyser where the proton NMR is analysed through Bruker Avance III, 400MHz with 9.4 Tesla super-conducting Magnet and operation temperature 360°C in SAIF-STIC, Kochi. The infrared spectrum for the complexes is done in the range of 4500-500 cm^{-1} in the Nicolet 6700FT-IR Spectrophotometer using KBr pellet in Bharathiar University, Coimbatore. Biological studies were done against both gram positive and negative bacterial strains and fungal strains using the Sabrouds dextrose agar medium for the culture and disc diffusion method is followed.

EXPERIMENTAL SECTION

General procedure for the synthesis of 2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta [*b*] indole (3).

An appropriate 1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole (**1**, 0.001 mol), was added to 10 mL of 5% alc.KOH (Potassium hydroxide in ethanol) and 4-methyl-benzaldehyde (**2**, 0.001 mol). The mixture was allowed to stir for 24 hours. At the end of the period the mixture was added to ice crush which gives a yellow

solid mass. The precipitated product was filtered off, washed with distilled water and dried. Using petroleum ether:ethyl acetate (98:2) as eluent the yellow solid mass was purified by column chromatography over silica gel which yields the corresponding 2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole (**3**).

8-methyl-2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole (3a)

Yellow solid; yield: 85%; m.p.142°C; IR (KBr, cm-1) ν max: 3331 (N-H), 1690 (C=O); 3023 (=CH-); ^{1}H-NMR (400 MHz, $CDCl_3$) (ppm) δ H: 1.57-1.69 (m, 4H, C_4-H_2 and C_5-H_2); 2.31 (s, 3H, C_8-CH_3), 2.38 (s, 3H, $C_{4'}$-CH_3), 2.78-3.00 (m, 4H, C_3-H_2 and C_6-H_2), 6.91 (s, 1H, benzylic NH), 7.09-7.71 (m, 7H, C_7, C_9, C_{10}, $C_{2'}$, $C_{3'}$, $C_{5'}$, and $C_{6'}$ - H), 8.82 (s, 1H, Indole NH); Elemental analysis, Calculated: C- 83.85, H- 07.03, N- 04.25%; Found: C- 83.83, H- 07.07, N- 04.23%; which was compatible with the molecular formula $C_{23}H_{23}NO$.

10-methyl-2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole (3b)

Yellow solid; yield: 75%; m.p.138°C; IR (KBr, cm-1) ν max: 3315 (N-H), 1632 (C=O); 3051 (=CH-); ^{1}H-NMR (400 MHz, $CDCl_3$) (ppm) δ H: 1.75-1.88 (m, 4H, C_4-H_2 and C_5-H_2); 2.39 (s, 3H, C_{10}-CH_3), 2.50 (s, 3H, $C_{4'}$-CH_3), 3.01 (t, 2H, C_3-H_2), 3.29 (t, 2H, C_6-H_2), 6.91 (s, 1H, benzylic NH), 7.05-7.55 (m, 7H, C_7, C_8, C_9, $C_{2'}$, $C_{3'}$, $C_{5'}$, and $C_{6'}$ - H), 8.93 (s, 1H, Indole NH); Elemental analysis, Calculated: C- 83.85, H- 07.03, N- 04.25%; Found: C- 83.87, H- 07.00, N- 04.28%; which was compatible with the molecular formula $C_{23}H_{23}NO$.

2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole (3c)

Yellow solid; yield: 90%; m.p.141°C; IR (KBr, cm-1) ν max: 3322 (N-H), 1622 (C=O); 3050 (=CH-); ^{1}H-NMR (400 MHz, $CDCl_3$) (ppm) δ H: 1.74-1.88 (m, 4H, C_4-H_2 and C_5-H_2); 2.39 (s, 3H, $C_{4'}$-CH_3), 2.99 (t, 2H, C_3-H_2), 3.31 (m, 2H, C_6-H_2), 6.90 (s, 1H, benzylic NH), 7.12-7.71 (m, 7H, C_7, C_8, C_9,C_{10}, $C_{2'}$, $C_{3'}$, $C_{5'}$, and $C_{6'}$ - H), 9.00 (s, 1H, Indole NH); Elemental analysis, Calculated: C- 83.77, H- 06.71, N- 04.44%; Found: C- 83.75, H- 06.68, N- 04.49%; which was compatible with the molecular formula $C_{22}H_{21}NO$.

8-Chloro-2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole (3d)

Yellow solid; yield: 83%; m.p.148°C; IR (KBr, cm-1) ν max: 3301 (N-H), 1632 (C=O); 2929 (=CH-); ^{1}H-NMR (400 MHz, $CDCl_3$) (ppm) δ H: 1.73-1.88 (m, 4H, C_4-H_2 and C_5-H_2); 2.39 (s, 3H, $C_{4'}$-CH_3), 3.00-3.04 (t, 2H, C_3-H_2), 3.22-3.25 (t, 2H, C_6-H_2), 6.92 (s, 1H, benzylic NH), 7.21-7.65 (m, 7H, C_7, C_9, C_{10}, $C_{2'}$, $C_{3'}$, $C_{5'}$, and $C_{6'}$ - H), 9.014 (s, 1H, Indole NH); Elemental analysis, Calculated: C- 75.52, H- 05.76, N- 04.00%; Found: C- 75.53, H- 05.74, N- 04.04%; which was compatible with the molecular formula $C_{22}H_{20}NOCl$.

General procedure for the synthesis of 2-hydroxy-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido [5',6':7,8]cycloocta[*b*]indoles (4)

A mixture of 2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole (**3**, 0.001 mol) which is dissolved in absolute ethanol (20 mL) and 0.001 mol of urea were refluxed for 1 hour. Reaction is monitored by TLC. The excess solvent was evaporated, and the crude reaction mixture was poured into crushed ice, yellow precipitate formed is filtered, washed with water and dried. The crude sample is purified by column chromatography with eluent (petroleum ether:ethyl acetate, 85:15) yields 2-hydroxy-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indoles **(4)**.

2-hydroxy-10-methyl-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indole (4a)

Yellow amorphous solid; yield: 69%; m.p.110°C; IR (KBr, cm-1) ν max: 3408 (N-H), 1519 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) (ppm) δ H: 2.28-2.38 (m, 8H, C_5, C_6, C_7, C_8-H_2), 2.40 (s, 3H, $C_{4'}$-CH_3), 2.54 (s, 3H, C_{10}-CH_3), 7.04-7.14 (m, 7H, C_9, C_{11}, C_{12}, $C_{2'}$, $C_{3'}$, $C_{5'}$ and $C_{6'}$-H), 8.65 (s, 1H, indole NH), 9.10 (s, 1H, C_2-OH); Elemental analysis: Calculated: C-75.08, H-06.27, N-11.37%; Found: C-75.10, H-06.26, N-11.36%; which was well-matched with the molecular formula $C_{24}H_{23}N_3O$.

2-hydroxy-12-methyl-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indole (4b)

Yellow solid; yield: 69%; m.p. 122°C; IR (KBr, cm-1) ν max: 3398 (N-H), 1544 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) (ppm) δ H: 1.75-1.85 (m, 4H, C_6 and C_7-H_2), 2.39 (s, 3H, $C_{4'}$-CH_3), 2.51 (s, 3H, C_{12}-CH_3), 3.00-3.03 (t, 2H, C_5-H_2), 3,27-3.31 (t, 2H, C_8-H_2), 6.99-7.55 (m, 7H, C_9, C_{10}, C_{11},$C_{2'}$, $C_{3'}$, $C_{5'}$ and $C_{6'}$-H), 8.88 (s, 1H, indole NH), 9.00 (s, 1H, C_2-OH); Elemental analysis: Calculated: C-75.08, H-06.27, N-11.37%; Found: C-75.08, H-06.27, N-11.36%; which was well-matched with the molecular formula $C_{24}H_{23}N_3O$.

2-hydroxy-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indole (4c)

Yellow amorphous solid; yield: 76%; m.p. 125°C; IR (KBr, cm-1) ν max: 3456 (N-H), 1567 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) (ppm) δ H: 1.18 -181 (m, 4H, C_6 and C_7-H_2), 2.31 (s, 3H, $C_{4'}$-CH_3), 2.92-3.24 (m, 4H, C_5 and C_8-H_2), 6.97-7.62 (m, 8H, C_9, C_{10}, C_{11}, C_{12}, $C_{2'}$, $C_{3'}$, $C_{5'}$ and $C_{6'}$-H), 8.95 (s, 1H, indole NH), 9.07 (s, 1H, C_2-OH); Elemental analysis: Calculated: C-77.72, H-5.95, N-11.82%; Found: C-77.74, H-5.95, N-11.80%; which was well-matched with the molecular formula $C_{23}H_{21}N_3O$.

10-chloro-2-hydroxy-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indole (4d)

Yellow amorphous solid; yield: 68%; m.p. 123°C; IR (KBr, cm-1) ν max: 3350 (N-H), 1540 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) (ppm) δ H: 1.46-1.86 (m, 4H, C_6 and C_7-H_2), 2.39 (s, 3H, $C_{4'}$-CH_3), 2.98-3.02 (t, 2H, C_5-H_2), 3.22-3.25 (t, 2H, C_8-H_2), 6.95-7.39 (m, 6H, C_{11}, C_{12}, $C_{2'}$, $C_{3'}$, $C_{5'}$ and $C_{6'}$-H), 7.65 (s 1H C_9-H), 9.06 (s, 1H, indole NH), 9.23 (s, 1H, C_2-OH); Elemental analysis: Calculated: C-70.61, H-05.17, N-10.77%; Found: C-70.83, H-05.19, N-10.77%; which was well-matched with the molecular formula $C_{23}H_{20}N_3OCl$.

General procedure for the synthesis of 2-mercapto-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido [5',6':7,8]cycloocta[*b*]indoles (5)

When appropriate 2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole (**3**, 0.001 mol) and thiourea (0.001 mol) in ethanol (5 mL) were refluxed for 1 hour, the intentional product is obtained. The completion of reaction is monitored through TLC. After the completion of reaction, the reaction mixture was cooled and poured into crushed ice, followed by dilute hydrochloric acid. The solid thus separated out was filtered, washed with water, dried and purified by column chromatography (petroleum ether:ethyl acetate, 90:10) and so it yields respective 2-mercapto-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indoles (**5**).

2-mercapto-10-Methyl-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indole (5a)

Yellow amorphous solid; yield: 76%; m.p.138°C; IR (KBr, cm-1) ν max: 3358 (N-H), 1532 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) (ppm) δ H: 1.65-2.19 (m, 4H, C_6 and C_7-H_2), 2.35 (s, 3H, $C_{4'}$-CH_3), 2.44 (s, 3H, C_{10}-CH_3), 2.74-2.90 (t, 2H, C_5 and C_8-H_2), 4.93 (s, 1H, C_2-SH) 7.06-7.28 (m, 6H, C_9, C_{11}, C_{12}, $C_{2'}$, $C_{3'}$, $C_{5'}$ and $C_{6'}$-H), 7.67 (s, 1H, C_9-H), 8.07 (s, 1H, indole NH); Elemental analysis: Calculated: C-74.78, H-06.01, N-10.89; Found: C-74.76, H-06.02, N-10.90%; which was well-matched with the molecular formula $C_{24}H_{23}N_3S$.

2-mercapto-12-Methyl-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indole (5b)

Yellow amorphous solid; yield: 71%; m.p. 128°C; IR (KBr, cm-1) ν max: 3666 (N-H), 1580 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) (ppm) δ H: 1.75-1.86 (m, 4H, C_6 andC_7), 2.35 (s, 3H, $C_{4'}$-CH_3), 2.50 (s, 3H, C_{12}-CH_3), 2.99-3.03 (t, 2H, C_5-H_2), 3.27-3.30 (t, 2H, C_8-H_2), 4.90 (s, 1H, C_2-SH), 7.04-7.55 (m, 7H, C_9, C_{10}, C_{11}, $C_{2'}$, $C_{3'}$, $C_{5'}$ and $C_{6'}$-H), 8.99 (s, 1H, indole NH); Elemental analysis: Calculated: C-74.78, H-06.01, N-10,89, S-8.32%; Found: C-74.77, H-06.02, N-10.91%; which was well-matched with the molecular formula $C_{24}H_{23}N_3S$.

2-mercapto-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indole (5c)

Yellow amorphous solid; yield: 71%; m.p. 103°C; IR (KBr, cm-1) ν max: 3294 (N-H), 1543 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) (ppm) δ H: 1.67-1.70 (p, 2H, C_6-H_2) 1.74-1.81 (p, 2H, C_7-H_2), 2.29 (s, 3H, $C_{4'}$-CH_3) 2.92-2.96 (t, 2H, C_5-H_2), 3.21-3.24 (t, 2H, C_8-H_2), 4.85 (s, 1H, C_2-SH), 7.05-7.12 (m, 4H, $C_{2'}$, $C_{3'}$, $C_{5'}$ and $C_{6'}$-H) 7.25-7.64 (m, 4H, C_9,

C_{10}, C_{11} and C_{12}), 8.95 (s, 1H, indole NH); Elemental analysis: Calculated: C-74.36, H-05.69, N-11.32; Found: C-74.36, H-05.67, N-11.32; which was well-matched with the molecular formula $C_{23}H_{21}N_3S$.

10-Chloro-2-mercapto-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indole (5d)

Yellow amorphous solid; yield: 73%; m.p. 189°C; IR (KBr, cm-1) ν max: 3341 (N-H), 1544 (C=N); 1H NMR (400 MHz, $CDCl_3$) (ppm) δ H: 1.73-1.80 (p, 2H, C_6-H_2) 1.82-1.88 (p, 2H, C_7-H_2), 2.36 (s, 3H, $C_{4'}$-CH_3), 2.98-3.02 (t, 2H, C_5-H_2), 3.22-2.25 (t, 2H, C_8-H_2), 4.88 (s, 1H, C_2-SH), 7.17-7.33 (m, 7H, C_9, C_{11}, C_{12}, $C_{2'}$, $C_{3'}$, $C_{5'}$ and $C_{6'}$-H), 9.07 (s, 1H, indole NH); Elemental analysis: Calculated: C-68.05, H-04.96, N-10.35%; Found: C-68.05, H-04.96, N-10.32%; which was well-matched with the molecular formula $C_{23}H_{20}N_3SCl$.

Procedure for biological study

Prepared compounds were subjected to the microbial studies to view their antimicrobial activity [7]. All the bacterial cultures were subjected for the analysis of vulnerability / resistance pattern to test samples by disc diffusion method (Bauer *et al*., 1996) using Mueller Hinton Agar medium (Cat. No. M1084, HiMedia, India) for bacteria and Sabrouds Dextrose Agar medium for fungi, Sterile medium was dispensed into sterile petri dishes. Broth cultures (24 hours) of the bacteria and fungi (48 hours) were used as inoculums. Using sterile cotton swab the test organisms were swabbed over the surface of the agar plate aseptically. In each of these plates, wells (10 mm) were cut out using sterile cork borer. The samples were dissolved in the solvent ethanol in different concentration (20-80 µg/ml) of the sample was loaded into the wells. Incubate the plates at 37°C for 24 hours in upright position of the plates. After the incubation, the diameters of inhibition zones were observed. If the zone is observed, the inhibition zone was compared with the Performance Standards for Antimicrobial disk Susceptibility Tests CLSI vol. 25 No1 Jan. 2005 (Chart of Kirby-Bauer sensitivity method modified in July 1966 (Scherring Corporation, U.S.A., Bloomfield, New Jersey) and classified as resistant, intermediate and sensitive. The intermediate strains were also scored as resistant.

The antibacterial activity of the compounds **4(a-d)** and **5(a-d)** was screened against the following species of both gram-negative and positive bacteria namely *Aeromonas hydrophila, Serratia marcescens, Acinetobacter baumanii, Pseudomonas aeruginosa* and *Bacillus licheniform,* respectively by the disc diffusion method using Mueller Hinton agar nutrient as the medium [8]. The antifungal activities were screened for the organisms *Aspergillus niger* and *Candidia albicans* and by the disc diffusion method cultured on Sabrouds dextrose agar as medium. For bacterial and fungal strains, Streptomycin and Nystatin are used as standards respectively and their zone of inhibition values are compared.

RESULTS AND DISCUSSION

Chemistry

Indole derivatives have also been extensively used in polymer industries. Polymers containing a carbazole moiety such as poly (N-vinylcarbazole) have been used as multifunctional materials viz., photoconductive [9], non-linear optical [10], electro-luminescent materials [11] and photorefractive [12-21]. Due to the activities of the above said compounds are being prepared by various techniques including one pot synthesis. Earlier synthetic routes towards the alicyclic of hetero annulated compounds are done by ring closure method [22]. The recent advancement as well as efforts made such as benzannulation [23], Fischer indolization [24], modified Nenitzescu reaction [25], cycloaddition reaction [26], cycloaromatisation [27], etc.

A simple method of synthesis for the construction of new-fangled organic compound is adopted here which yields in significant quantity, which also reduces the effort and uncomplicated steps are being followed in the synthesis part. Using the reported method [28], the precursor cycloocta[*b*]indole **(1)** is prepared by using cyclooctanone. cycloocta[*b*]indole **(1)** and 4-methyl benzaldehyde **(2)** is used for the synthesis of condensed product, which is commercially available.

By the condensation [29] of 4-methyl-benzaldehyde with 8-methyl-1-oxo-1,2,3,4,5,6-hexahydrocycloocta [*b*]indole **(1a)** in the alkaline condition (KOH in ethanol) furnishes 8-methyl-2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole **(3a)** that can be seen in the reaction **Scheme: 1.** The product compound **(3a)** is yellow amorphous solid that has melting point of 142°C where as the yield is

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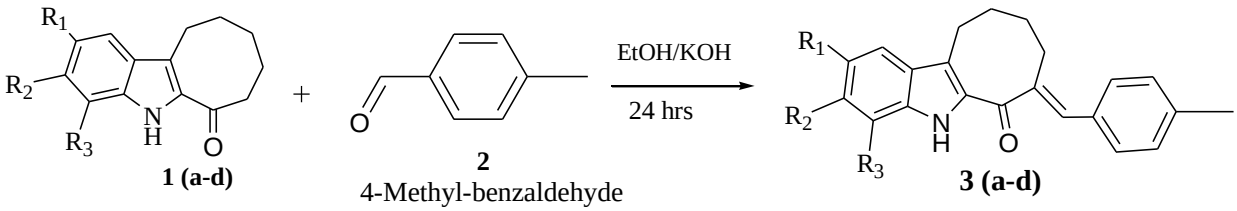
achieved about 85%. The IR spectrum for **(3a)** shows a strong band at 3331 cm^{-1} a typical band for –NH group where as for (C=O) band appears at 1690 cm^{-1}. A weak band at 3023 cm^{-1} is assigned to the (=CH-) group. Compound **(3a)** can be justified with ^{1}H-NMR (δ values in ppm) spectrum which gives particulars as follow; a four proton multiplet resonates in the region δ 1.57-1.69 assigned for C_4-H_2 and C_2-H_2. Two singlets for three proton appear in the region of δ 2.31 and 2.38 assigned for C_8-CH_3 and $C_{4'}$-CH_3; a four proton multiplet for C_3-H_2 and C_6- H_2 is present at δ 2.78-3.00; δ 6.91 is a peak of benzylic NH which is singlet; the aromatic protons of benzylidiene and indole moieties shows a signal at δ 7.09-7.71 as a multiplet C_7, C_9, C_{10}, $C_{2'}$, $C_{3'}$, $C_{5'}$, and $C_{6'}$ - 7H, a less intense peak at δ 8.82 a singlet is for indole NH. Hence the condensation product **(3a)** can be assigned with molecular formula in accordance with the elemental analysis ($C_{23}H_{23}NO$) and their calculated value and found value are matching in finely. **3b, 3c** and **3d** compounds have been prepared respectively, by using appropriate **1b, 1c** and **1d** for the reaction with 4-methyl-benzylidene with yield 75-90 % and their spectra are associated to their structure.

Scheme: 1

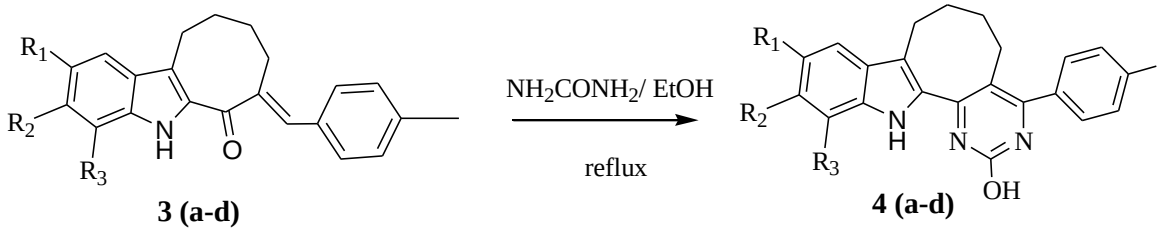


1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole

2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole

A classic reactions has been proceeded using the condensed product **(3a)** as follows**,** when 8-methyl-2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole **(3a)** reacts with urea it results in a pyrimido compound 2-hydroxy-10-methyl-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido [5',6':7,8]cycloocta [*b*]indole **(4a)** that can be seen in **Scheme: 2**. Compound is yellow in colour with melting point 110 °C. In the IR spectrum of **(4a)**, instead of stretching frequency of carbonyl group (C=O), a new signal for C=N has been appeared at 1519 cm^{-1}, and the NH gives a band at 3408 cm^{-1}. The ^{1}H-NMR spectrum provides the specifics about the hydrogen atoms as follows, at δ 1.32 singlet for three protons of $C_{4'}$-CH_3, a singlet at δ 1.49 for three methyl protons (C_{10}-CH_3), at δ 1.85-1.94 which is pentet due to the two protons of cyclooctanone at the position C_7-H_2, while a multiplet at the range δ 2.22 for the two protons at the position C_6-H_2, triplet signal for two protons emerges at δ 3.18-3.22 for C_5-H_2, another triplet for C_8-H_2 at δ 3.29-3.34, a range of aromatic multiplet signal δ 7.04-7.14 for 7H of C_9, C_{11}, C_{12}, $C_{2'}$, $C_{3'}$, $C_{5'}$ and $C_{6'}$-H, where as the presence of signal for one proton at δ 8.65 which is assignable for indole NH, and another singlet is there for one proton occurs in the region δ 9.18 due to the proton of OH. Likewise **(3b-d)** react with urea to give appropriate products such as **(4b-d)** with yield 75-85 % and their spectra are corresponding to their structure.

Scheme: 2



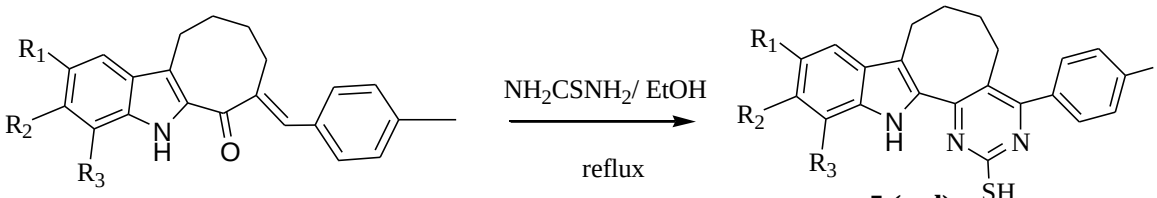
2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole

2-hydroxy-8-methyl-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[b]indole

In the reaction of 8-methyl-2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole **(3a)** with thiourea, mercaptopyrimido derivative namely 2-mercapto-10-methyl-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indole **(5a)** is produced as shown in the **Scheme: 3** with 76% of yield which is a pale yellow amorphous solid with the melting point of 138°C. IR spectrum augments the result of

formation pretended compound, accompanied by the fading of carbonyl group signal (C=O) and the appearance of a signal (C=N) at 1532 cm^{-1} and emergence of another characteristic signal for indole NH at 3358 cm^{-1}. The enhancement is obtained through the ^{1}H-NMR spectrum since the multiplet at δ 1.42-1.48 for two protons of C_6 and another multiplet of two protons of C_7; at δ 2.15-2.19 a triplet signal appears for C_5-H_2; a sharp singlet signal for three protons δ $C_{4'}$-CH_3 at δ 2.35; another signal which is singlet δ 2.44 is assignable for three protons of methyl group of C_{10}-CH_3; for C_8-H_2 a triplet appears at δ 2.83-2.90; for proton of mercapto group (-SH) singlet signal appears at 4.93; multiplet for 7H resonates in the aromatic regions at the range δ 7.06-7.28 (C_9, C_{11}, C_{12}, $C_{2'}$, $C_{3'}$, $C_{5'}$ and $C_{6'}$- H); for indole NH a weak singlet appears at δ 8.07 characteristically. **(3b-d)** compounds react with thiourea and give the respective products **(5b-d)** with yield about 70-75% and they are yellow amorphous solids with apt melting point. Their structures are assignable in fair manner as their spectral values are relatively appropriate.

Scheme: 3



3 (a-d) **5 (a-d)**

2-(4'-methyl)-benzylidene-1-oxo-1,2,3,4,5,6-hexahydrocycloocta[*b*]indole

2-hydroxy-8-methyl-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[b]indole

a: R1=CH3, R2=H, R3=H; b: R1=H, R2=H, R3=CH3; c: R1=H, R2=H, R3=H; d: R1=Cl, R2=H, R3=H

Biological Activities

The usage of medicines represents a lengthy history of human interactions with the environment. Plants used for traditional medicine contain a wide range of substances that can be used to treat chronic as well as infectious diseases (Duraipandiyan et al., 2006). Carbazole and other indole fused compounds represent new and remarkable options. In the large number of indole alkaloids, several important drugs such as *Murraya koenigii* (*Rutaceae*) popularly known in India as the curry leaf plant has been found to be a wealthy and rewarding source [30]. Recently carbazole alkaloid, glycoborine, etc., were isolated from the roots of *glycosmis arborea* [31]. Some mirco organisms are also useful in isolation of alkaloid. Hyellazole isolated from the blue-green algae, *Hyella caespitosa,* represent the first carbazole alkaloid of the marine origin. Carbazole alkaloids isolated from the leaves of this plant elicit anti inflammatory, antioxidant, antimicrobial and topoisomerase I and topoisomerase II inhibition activities. With interest as synthetic targets, indole alkaloids attract more researchers, as many of their derivatives exhibit expansive range of probable biological activities.

It is necessary to construct or synthesis the desired chemical components analogue to the plant materials for further treatment and other medicinal purpose with interest as synthetic targets. Heterocycles (Katritzky *et al*. 1996) made up an exceedingly important class of compounds in which more than half of all known organic compounds are heterocycles. Diverse heterocyclic compounds and their derivatives with potent antibacterial and antifungal activity are obtained and a number of papers have been reported concerning the synthesis of pyrimidine derivatives [32]. Here the report with the pyrimidine and indole fused synthetic parts are being presented with several series of biologically active compounds and have evaluated on their biological activity.

For the compounds series **(4a-d)** and **(5a-d)** the biological activity that is to say anti bacterial and antifungal activities were made and referred in the inhibition zones [33] form, that was developed biologically, and the activity was inferred to be moderately active for both bacteria and fungi, which can be seen in **Table: 1** and **2**. According to that, the indole fused pyrimido compounds, and mercaptopyrimido compounds, viz., 2-hydroxy-12-methyl-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indole **(4b)** and 2-mercapto-12-Methyl-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indole **(5b)** show more potency to counter the bacterial and fungal organisms. All compounds exhibits better activity against *Serratia* and *Aspergillus* than other bacterial strains, has been seeing at higher concentration levels; and nearer activity is noted for fungal strains. In the case of comparison between two species, both pyrimido and

mercaptopyrimido compounds exhibits logically more active against fungal strains than bacterial strains in lower concentrations too. Towards the increment of concentration that are assigned for the series **(a-d), Tables: 1** and **2** reveal the increasing action of compounds against micro organisms. In general, opposition of all the subjected compounds against the micro organisms is being reasonably active comparatively in the increasing concentration.

Table: 1 Antibacterial and Antifungal activity of 4(a-d)

S.No	Name of the Organism	Zone of Inhibition in mm																			
		4a (µg/ml)					4b (µg/ml)					4c (µg/ml)					4d (µg/ml)				
		R	20	40	60	80	R	20	40	60	80	R	20	40	60	80	R	20	40	60	80
1	*Pseudomonas aeruginosa*	20	4	7	8	9	22	4	5	8	9	21	21	4	6	7	21	4	4	6	10
2	*Aeromonas hydrophila*	21	4	8	8	10	21	5	8	9	10	19	3	3	5	9	20	4	6	8	10
3	*Acinetobacter baumannii*	21	5	6	8	10	22	4	7	8	10	22	2	3	5	8	20	5	6	9	10
4	*Serratia marcescens*	18	4	7	9	9	19	5	6	9	11	19	5	5	6	8	18	4	7	8	9
5	*Bacillus licheniformis*	20	5	6	7	9	20	4	6	8	9	21	3	4	6	7	19	4	6	9	10
6	*Aspergillus niger*	21	4	7	7	11	20	5	7	10	11	21	4	6	8	8	22	4	6	7	9
7	*Candida albicans*	20	5	6	9	10	22	5	6	8	10	21	4	5	9	10	22	4	5	9	10

Table: 2 Antibacterial and Antifungal activity of 5(a-d)

S.No	Name of the Organism	Zone of Inhibition in mm																			
		5a (µg/ml)					5b (µg/ml)					5c (µg/ml)					5d (µg/ml)				
		R	20	40	60	80	R	20	40	60	80	R	20	40	60	80	R	20	40	60	80
1	*Pseudomonas aeruginosa*	21	5	6	7	10	19	4	6	8	10	22	4	6	8	11	21	4	6	9	11
2	*Aeromonas hydrophila*	20	4	7	9	11	20	4	7	9	11	21	4	6	8	10	20	4	7	8	10
3	*Acinetobacter baumannii*	21	4	5	8	9	21	4	6	8	9	22	4	5	6	8	21	4	6	9	10
4	*Serratia marcescens*	20	4	6	7	10	21	4	6	8	10	20	4	6	7	10	22	4	7	8	10
5	*Bacillus licheniformis*	21	5	6	8	10	20	4	6	8	9	20	5	6	8	10	21	5	6	7	11
6	*Aspergillus niger*	20	5	6	9	10	19	4	6	7	10	20	5	6	9	11	22	5	7	9	10
7	*Candida albicans*	19	5	7	9	10	22	5	6	8	9	20	4	7	8	9	19	4	5	8	9

***R-** inhibition zone of the standards (streptomycin and nystatin) used against bacterial and fungal strains respectively.

CONCLUSION

It has been become public about a simple and new efficient route for the production and application of biologically capable and significant compounds. Using cyclooct[*b*]indole and 4- methyl-benzyaldehyde, the condensed product **(3)** is produced which acts as a parent for the preparation of further compounds i.e., 2-hydroxy-pyrimidocycloocta[*b*]indole and 2-mercaptopyrimidocycloocta[*b*]indole derivatives. With cycloocta[*b*]indole derivatives 4-methyl-benzaldehyde is employed to compress and being given the compound **(3)**, which is the preliminary step to make a favourable condition for further reaction and this

strategy allows the same to react with urea and thiourea that results in 2-hydroxy-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydro-pyrimido[5',6':7,8]cycloocta[*b*]indoles **(4)** and 2-mercapto-4-(4'-methyl)-phenyl-5,6,7,8-tetrahydropyrimido[5',6':7,8]cycloocta[*b*]indoles **(5)** respectively. The procedure is less complicated and yields about more than 60% fairly. The biological results show a remarkable action towards micro organisms as the increment of concentration of the compounds that are assigned for the series **(a-d)** the **Tables**. **1** and **2** reveal the increasing action of compounds against micro organisms and it could be assigned for the functional group such as e.g. pyrimido structures or six member heterocyclic ring annulations. This may lead us to assume towards the other biological activities such as cytotoxicity, antitumour activity, protein docking, etc., as they can interact with microorganisms.

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REFERENCES

[1] Michael JP, Nat Prod Rep. 2003; 20: 458-475.
[2] Michael J, Nat Prod Rep. 2004; 21: 650-668.
[3] Herbert RB, Nat Prod Rep. 2003; 20: 494-508.
[4] Bhattacharayya P, and Chakraborty DP, (Eds. W. Herz, H Grisebach, G. W. Kirby, C. Tamm) Springer Verlag, 1987; 52: 159.
[5] Herz Eds W, Grisebach H, Kirby GW and Tamm C, Springer Verlag 1991; 57: 71.
[6] Chakraborty DP, Ed. A. Brossi, Academic Press, New York, 1993; 44: 257.
[7] Salih N, Salimon J, Yousif E, Arabian. J. Chem 2016; 9: S781-S786
[8] Hoegl, H, J. Phys. Chem. 1965; 69: 755-756.
[9] Tamura K, Paodias AB, Hall HK, Peyghambarian N, Appl. Phys. Lett. 1992; 60: 1803-1805.
[10] Moemev WE, Silence, Chem. Rev. 1994; 94: 127-155.
[11] Johnson GE, McGrane KM, Stolka M, Pure and Appl. Chem. 1995; 67: 175-182.
[12] Evans PA, Holmes AB, Collins I, Raithby PR, Russell K, J. Chem. Soc. Chem. Commute 1995; 2325.
[13] Zhang YD, Wang L, Wada T, Sasabe H, Macromolecules 1996; 29: 1569-1573.
[14] Costa VD, Moigne JL, Oswald L, Pham TA, Thierry A, Macromolecules 1998; 31: 1635-1643.
[15] Diaz-Garcia MA, Wright D, Casperson JD, Smith B, Glazer E, Moerner WE, Sukhomlinova LI, Twieg RJ, Chem. Mater. 1999; 11: 1784-1791.
[16] Kim DW, Moon H, Park SY, Hong SI, React. Funct. Polym 1999; 42: 73-86.
[17] Chen JP, Natansohn A, Macromolecules 1999; 32: 3171-3177.
[18] Bouguettaya M, Valliere M, Chevrot C, J. Appl. Polym. Sci. 1999; 73: 1483-1492.
[19] Prudhomme DP, Wang Z, Rizzo CJ, J. Org. Chem. 1997; 62: 8257-8260.
[20] Wang Z, Prudhomme DP, Buck JR, Park M, Rizzo CJ, J. Org. Chem. 2000; 65: 5969-5985.
[21] Yamuna E, Zeller M, Rajendra Prasad KJ, Tetrahedron Letters 2011; 52: 1649-1652.
[22] (a) Kano S, Sugino E, Shibuya S, Hibino S, J Org Chem 1981; 46: 2979-2981.
(b) Bergman J, Pelcman B, Tetrahedron 1988; 44: 5215.
(c) Boogaard AT, Pandit UK, Koomen GJ, Chemsrc. 1944; 50: 4811-4828.
[23] (a) Maetarello L, Joseph D, and Kirsch G, Heterocycles 1996; 43: 367-379.
(b) Dufour F, Kirsch G, Synlett 2006; 07: 1021-1022.
(c) Hong BC, Jiang YF, Chang YL, Lee SJ, J. Chin. Chem. Soc. 2006; 53: 647-662.
[24] Asche C, Frank W, Albert A, Kucklaender U, Bioorg Med Chem. 2005; 13: 819-837.
[25] (a) Moody CJ, J Chem Soc, Perkin Trans 1 1985; 2505-2508.
(b) Gribble GW, Keavy DJ, Davis DA, Saulnier MG, Pelcman B, Barden TC, Sibi MP, Olson ER, BelBruno JJ, J Org Chem 1992; 57: 5878-5891.
(c) Sha CK, Chuang KS, Wey SJ, J Chem Soc, Perkin Trans. 1987; 1: 977-980.
(d) Martinez-Esperon MF, Rodriguez D, Castedo L, Saa C, Tetrahedron 2006; 62: 3843-3855.
(e) Mal D, Senapati BK, Pahari P, Tetrahedron 2007; 63: 3768-3781.
[26] (a) Shi C, Wang KK, J Org Chem 1998; 63: 3517-3520.
(b) Schmittel M, Rodriguez D, Steffen JP, Angew Chem Int Ed 2000; 39: 2148-2152.
[27] Kapil RS, The Alkaloids 1971; 13: 273-302.
[28] Sangeetha V, Rajendra Prasad KJ, Heterocycl. comm., 2002; 8(1): 65-70.

[29] Sangeetha V, Rajendra Prasad KJ, Asian J chem., 2004; 16(2): 1165.
[30] Bhattacharyya P, Chowdhury BK, J. Nat. prod. 1985; 48: 465-466.
[31] Mojtahedi MM, Saidi MR, Shirzi JS, Bolourtchian M, Synth. Commun 2002; 32: 851-56.
[32] Bhattacharjee MK, J. Antibiot, 2015; 68: 657-659.
[33] Bauer AW, Kirby WMM, Sherries JC, Truck M, American. J. Clin. Pathol 1966; 36: 493-496.