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Dihydropyrimidines as Precursors for Synthesizing of Oxoketene *gem*-Dithiol and 1,2-Dithiol-3-Thione, a Facile Synthesis and Convenient Reaction Transformations

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Abstract

In the present work the authors could synthesize the substrates oxoketene *gem*-dithols **5**, ketene dithioacetal **6** and 1,2-dithiol-3-thione **39** from compounds bearing both nucleus indole and dihydropyrimidines together due to their biological and pharmacological activities. In this paper, and as a result of biological and pharmacological activities of oxoketene *gem*-dithiols, ketene dithioacetal and/or 1,2-dithiol-3-thione; we synthesized various derivatives of them via indole and dihydropyrimidine in the form of either condensed or fused derivatives. We used ecofriendly methods such as pure orange juice as a green solvent and as an acid catalyst in the same time to prepare, 1-[2-imino-4-(1*H*-indol-3-yl)-6-methyl-1,2,3,4-tetrahydropyrimidin-5-yl]-ethan-1-one **4a** and/or 1-[4-(1*H*-Indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]-ethan-1-one **4b**. Subsequently, the substrate **4b** was treated with different reagents to afford, 1-(4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3,3-dimercaptoprop-2-en-1-one **5** and/or 1-(4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3,3-bis(methylthio)prop-2-en-1-one **6**. Compounds **5** and/or **6** were used as synthons to get various heterocyclic compounds such as 3-(4-(1*H*-indol-3-yl)-6-methyl-2-(piperidin-1-yl)-1,4-dihydropyrimidine-5-carbonyl)-2-thioxochroman-4-one **16** and/or 4'-(1*H*-indol-3-yl)-2-mercapto-6'-methyl-6-(methylthio)-2'-thioxo-1',2',3',4'-tetrahydro-[4,5'-bipyrimidine]-5-carbaldehyde **18**. The newly synthesized compounds have been in vitro examined as antimicrobial agents, and some of them showed a promising activity. All newly synthesized compounds have been characterized by means of elemental analyses, IR, ^{1}H-NMR and MS.

Keywords α-Oxoketene *gem*-dithiols; dihydropyrimidine; 1,2-dithiol-3-thione; indole; 3-indole aldehyde; Kneovenagel's condensation.

1. Introduction

Nitrogen and sulfur containing heterocycles [1] like pyrimidines, indole, dithiol and thione derivatives [2] play an important role in medicinal chemistry, biological and industrial fields.[3,4] Pyrimidines have wide spectrum activity against DNA and RNA viruses such as polio herpes viruses, diuretic, antitumor, anti HIV, cardiovascular, anti-carcinogenic and anti-inflammatory.[5-11] They [5] can be used as antibacterial, anticancer, antifungal, and antiviral.[12-15] Dihydropyrimidines (DHPMs) can serve as antioxidant, and orally active antihypertensive agents.[16] It was reported that, novel heterocycles containing indole ring have antimicrobial activities against the bacteria Staphylococcus aureus, Salmonella typhi, Escherichia coli and two fungal species Candida albicans, Aspergillus niger.[17] On the other hand indole containing heterocycles were used as anti-inflammatory, anticonvulsant agents, antitumor agents in the human cell line and cardioselective anti-ischemic ATP-sensitive potassium channel (KATP) opener activity.[18,19] Anticancer activity of various tricyclic and tetracyclic indoles, against human

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nasopharyngeal carcinoma (HONE-1) and gastric adenocarcinoma (NUGC-3) cell lines were studied by Hong et al.[3,20] Khaledi et al [21], synthesized some indole derivatives which have antioxidant activities on DPPH radical scavenging and inhibition of lipid peroxidation.[21] The in vitro cytotoxic activities of the compounds bearing indole nucleus were evaluated against HCT-116 (human colon cancer cell line) and MCF-7 (estrogen dependent human breast cancer cell line). Serotonin which is derived from indole presents in the gastrointestinal tract (GI tract), blood platelets, and the central nervous system (CNS) of animals and humans, adds happiness. Some indole derivatives used to treat different types of cancer like Hodgkin's lymphoma, testicular cancer, non-small cell lung cancer, bladder cancer and brain cancer.[3,21] Indole-substituted compounds which are a nootropic drug developed for the treatment of Alzheimer's disease (AD) and they are used as potent non-steroidal anti-inflammatory agents which are more active than aspirin in the prophylactic and therapeutic adjuvant-induced polyarthritis models of chronic inflammation.[22] Several organic dyes, pigments and food colourants are derived from indole.[23] Spirooxoindoles have been synthesized and used in agriculture field as plant-produced hormones affecting plant growth including bud formation and root initiation beside to their significant antifungal activities.[24,25] In addition, moieties containing 3*H*-1,2-dithiol-3-thiones [26] rings display widespread biological activities and were used as chemo-therapeutic agents against liver cancer. Also, they [26] have been proved as a useful starting materials for synthesis of variety of heterocyclic compounds.[27] Extensive studies have been carried out on oltipraz (4-methyl-5-pyrazinyl-3*H*-1,2-dithiole-3-thione) and showed that; oltipraz possesses remarkable activity to inhibit HIV-1 (AIDES) virus.[28] Here in we have been collected the biological properties of ketene *gem*-dithiols, ketene diothioacetals and/or 1,2-dithiol-3-thiones together with that of dihydropyrimidine and/or indole nucleus in a one compound in the hope of obtaining a more potent and wide spectrum biologically active precursors and studying their behavior toward some nucleophiles and electrophiles under acidic and/or basic medium hoping for the construction of various heterocyclic systems.

2. Experimental

All melting points are uncorrected and were determined on Kofler melting point apparatus. The progress of the reactions was followed up by TLC technique. IR spectra were determined with Shimadzu IR 408 infrared spectrophotometer using KBr wafer technique. ^{1}HNMR spectra were recorded on Perkin Elmer 300 MHz spectrometer using TMS as an internal reference and chemical shifts are expressed as δ. The electron impact mass spectra were obtained at 70 eV using Shimadzu QP-2010 Plus mass spectrometer. Biological activity was carried out at microbiology lab., Cairo University

Synthesis of 1-[2-imino-4-(1*H*-indol-3-yl)-6-methyl-1,2,3,4-tetrahydropyrimidin-5-yl]-ethan-1-one (4a)

(0.145 gm, 0.001 mol) Of 3-indole aldehyde **1** was treated with (0.1 ml, 0.001 mol) of acetylacetone **2** and (0.059 gm, 0.001 mol) of guanidine **3a** in (20 ml) pure orange juice. The mixture was heated under reflux for two hours, and it was left to cool, then it was poured over ice and left over night to settle. The mixture was filtered and the product was collected. The yield: 75%, M. P. 150 ^{o}C, colour: orange, recrystallization from: benzene. Mass spectrum m/e (I, %) 268 ($M^{+\cdot}$, 40), (117, 100). IR (KBr): ν (cm^{-1}): 3404 (-NH), 1632 (C=O). ^{1}HNMR (DMSO): δ (ppm.): 2.30 (s, 3H, CH_3), 2.36 (s, 3H, $COCH_3$); 3.31 (s, 1H, CH), 7.18-7.59 (m, aromatic protons), 8.03 (s, 1H, NH), 8.27 (s, 1H, NH), 9.94 (s, 1H, NH), 12.11 (s, 1H, NH), Elemental analysis for $C_{15}H_{16}ON_4$ (268.301); Calcd: C, 67.14; H, 6.01; N, 20.88. Found: C, 67.16; H, 6.05; N, 20.78.

Synthesis of 1-[4-(1*H*-Indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]-ethan-1-one (4b)

(0.145 gm, 0.001 mol) Of 3-indole aldehyde **1** reacted with (0.1 ml, 0.001 mol) of acetylacetone **2** and (0.076 gm, 0.001 mol) of thiourea **3b** in (20 ml) pure orange juice, the mixture was heated under reflux for three hours, then it was cooled and poured over ice, it was left over night to settle. The mixture was filtered, and the product was collected. The yield: 70%, M. P. 210 ^{o}C, colour: red, recrystallization from: benzene. Mass spectrum m/e (I, %) 285 ($M^{+\cdot}$, 60), (68, 100). IR (KBr): ν (cm^{-1}): 3404 (-NH), 1632 (C=O). ^{1}HNMR (DMSO): δ (ppm.): 2.10 (s, 3H, CH_3), 2.29 (s, 3H, $COCH_3$); 3.32 (s, 1H, CH), 6.28-7.52 (m, aromatic protons), 8.27 (s, 1H, NH), 9.94 (s, 1H, NH), 10.69 (s, 1H, NH), Elemental analysis for $C_{15}H_{15}N_3OS$, (285.35) Calcd: C, 63.13; H, 5.30; N, 14.73; S, 11.24 Found: C, 63.15; H, 5.29; N, 14.73; S, 11.32.

Synthesis of 1-(4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3,3-dimercaptoprop-2-en-1-one (5)

Carbon disulfide (0.06 ml, 0.001 mol) was added to (0.285 gm, 0.001 mol) dihydropyrimidine **4b**, in (20 ml) dry benzene; the mixture was cooled to 0-5 ^{o}C in an ice bath. Potassium tertiary butoxide (0.112

gm, 0.001 mol) was added gradually to the cooled mixture with continuous shaking. After complete addition of potassium tertiary butoxide, the mixture was left over night in fridge; cold water was then added with continuous shaking of the previously prepared mixture. The mixture was agitated vigorously and it was poured in a separating funnel where it divided into two layers benzene layer and aqueous layer. The aqueous layer was washed several times with petroleum ether 40/60 and then it was acidified with cold concentrated sulfuric acid. The mixture was left in the fridge to settle and collect. After complete precipitation the mixture was filtered off and the precipitate was collected and left aside to dry. The yield: 91.6%, M. P. 150 ^{o}C, colour: red, recrystallization from: benzene. Mass spectrum m/e (I, %) 361 ($M^{+\cdot}$, 10), (64, 100). IR (KBr): ν (cm^{-1}): 3167 (-NH), 1634 (C=O). ^{1}HNMR (DMSO): δ (ppm.): 1.35 (s, 2H, 2SH), 2.10 (s, 3H, CH_3), 3.41 (s, 1H, CH), 6.05 (s, 1H, ylidenic CH), 7.00-8.09 (m, aromatic protons), 8.25 (s, 1H, NH), 8.27 (s, 1H, NH), 9.93 (s, 1H, NH), Elemental analysis for $C_{16}H_{15}N_3OS_3$ (361.50) Calcd: C, 53.16; H, 4.18; N, 11.62; S, 26.61 Found: C, 53.15; H, 4.16; N, 11.70; S, 26.66.

Synthesis of 1-(4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3,3-bis(methylthio)prop-2-en-1-one (6)

Carbon disulfide (0.009 ml, 0.0015 mol) was added to (0.285 gm, 0.001 mol) compound **4b** in (50 ml) dry benzene and the mixture was cooled to 0-5 ^{o}C in an ice bath. Potassium tertiary butoxide (0.112 gm, 0.001 mol) was added gradually to the cooled mixture with continuous shaking. After complete addition of potassium tertiary butoxide, the mixture was left over night in the fridge then methyl iodide (0.311 ml, 0.005 mol) was added to the previous potassium salt and stirred at temperature 0 ^{o}C in ice path for 4 hrs. The so formed product was filtered and washed with petroleum ether 40/60 giving the required compound **5b**. The yield: 75%, M. P. 175 ^{o}C, colour: dark brown, recrystallization from: benzene. Mass spectrum m/e (I, %) 389 ($M^{+\cdot}$, 5), (64, 100). IR (KBr): ν (cm^{-1}): 3392 (-NH), 1635 (C=O). ^{1}HNMR (DMSO): δ (ppm.): 2.31 (s, 3H, CH_3), 2.64 (s, 6H, $2SCH_3$), 3.96 (s, 1H, CH), 6.05 (s, 1H, ylidenic CH), 6.81-7.39 (m, aromatic protons), 8.40 (s, 1H, HN), 8.42 (s, 1H, NH), 9.94 (s, 1H, NH), Elemental analysis for $C_{18}H_{19}N_3OS_3$ (389.55); Calcd: C, 55.50; H, 4.92; N, 10.79; S, 24.69 Found: C, 55.50; H, 4.89; N, 10.80; S, 24.83.

Synthesis of 5-(4-hydroxy-6-(1*H*-indol-3-yl)-2, 2-bis(methylthio)-3,4-dihydro-2*H*-pyran-4-yl)-4-(1*H*-indol-3-yl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione (11)

A mixture of compound **6** (0.389 gm, 0.001 mol) and 3-acetylindole **7** (0.159 gm, 0.001 mol) in (15 ml) DMSO in the presence of potassium hydroxide was stirred at 10-15 ^{o}C for 6 hrs. A cold diluted HCl was then added, the product precipitated and it was left aside to settle. The product was collected and washed several times with water and then it was left to dry. The yield: 68%, M. P. 170 ^{o}C, colour: brown, recrystallization from: benzene. Mass spectra m/e (I, %) 548 ($M^{+\cdot}$, 5), (64, 100). (IR (KBr): ν (cm^{-1}): 1236 (C=S), 1391 (SCH_3), 1012 (CH=C), 3399 (OH). ^{1}HNMR (DMSO): δ (ppm.): 2.31 (s, 3H, CH_3), 2.41 (s, 1H, OH), 2.45 (s, 2H, CH_2), 2.64 (s, 6H, $2SCH_3$), 3.68 (s, 1H, CH), 6.04 (s, 1H, ylidenic CH), 6.83-7.88 (m, aromatic protons + 1H, NH), 8.01 (s, 1H, NH), 8.04 (s, 1H, NH), 10.70 (s, 1H, NH), Elemental analysis for $C_{28}H_{28}N_4O_2S_3$ (548.74); Calcd: C, 61.29; H, 5.14; N, 10.21; S, 17.53 Found: C, 61.18; H, 5.32; N, 10.20; S, 17.44.

Synthesis of 3-(4-(1*H*-indol-3-yl)-6-methyl-2-(piperidin-1-yl)-1,4-dihydropyrimidine-5-carbonyl)-2-thioxochroman-4-one (16)

To (0.361 gm, 0.001 mol) of dithiol **5** and (0.106 ml, 0.001 mol) of salicylaldehyde **12** in (20 ml) THF was added (2 drops) of piperidine. The mixture was heated under reflux for 3 hrs. The solution was concentrated, few drops of ethanol were added to it to precipitate the solid product, and the so formed product was collected. The yield: 68%, M. P. 145 ^{o}C, colour: yellow, recrystallization from: ethanol/benzene. Mass spectrum m/e (I, %) 498 ($M^{+\cdot}$, 50), (285, 100). IR (KBr): ν (cm^{-1}): 3409 (-NH), 1635 (C=O), 1158 (C=S). ^{1}HNMR (DMSO): δ (ppm.): 1.20-1.80 (m, 11H, $5CH_2$ + 1H, CH), 2.80 (s, 3H, CH_3), 3.94 (s, 1H, CH), 6.82-7.53 (m, aromatic protons), 9.99 (s, 1H, NH), 10.70 (s, 1H, NH), Elemental analysis for $C_{28}H_{26}N_4O_3S$ (498.56) Calcd: C, 67.45; H, 5.26; N, 11.24; S, 6.43 Found: C, 67.43; H, 5.31; N, 11.27; S, 6.39.

Synthesis of 2-(4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbon-yl)-3,3-bis(methylthio)acrylaldehyde (17)

A solution of compound **6** (0.389 gm, 0.001 mol) in (20 ml) of DMF was stirred in ice path at 0 ^{o}C for 2 hrs in the presence of (5 ml) of $POCl_3$. Then it was triturated with a solution of potassium carbonate, effervescence took place. The solution was left aside to settle then it was filtered and the product was collected. The yield: 80%, M. P. >300 ^{o}C, colour: dark brown, recrystallization from: DMF. Mass

spectrum m/e (I, %) 417 ($M^{+\cdot}$, 40), (117, 100). IR (KBr): ν (cm^{-1}): 3286 (-NH), 1659 (C=O). ^{1}HNMR (DMSO): δ (ppm.): 2.64 (s, 3H, CH_3), 2.73 (s, 3H, SCH_3), 2.84 (s, 3H, SCH_3), 3.31 (s, 1H, CH), 6.81-7.56 (m, aromatic protons + 1H, NH), 9.22 (s, 1H, NH), 10.68 (s, 1H, NH), 11.80 (s, 1H, CHO), Elemental analysis for $C_{19}H_{19}O_2S_3N_3$ (417.56) Calcd: C, 54.65; H, 4.59; N, 10.06; S, 23.00 Found: C, 54.77; H, 4.52; N, 10.31; S, 23.17.

Synthesis of 4'-(1*H*-indol-3-yl)-2-mercapto-6'-methyl-6-(methylthio)-2'-thioxo-1',2',3',4'-tetrahydro-[4,5'-bipyrimidine]-5-carbaldehyde (18)

To a mixture of compound **17** (0.417 gm, 0.001 mol) and thiourea **3b** (0.076 gm, 0.001 mol) in (20 ml) acetonitrile was added potassium carbonate and then the mixture was heated under reflux for 4 hrs. The solution was concentrated and left to cool. The precipitated product was dissolved in water to do without potassium carbonate. The solution was filtered off and left to settle and the so formed adduct was collected. The yield: 75%, M. P. >300 °C, colour: brown, recrystallization from: DMF. Mass spectrum m/e (I, %) 427 ($M^{+\cdot}$, 2), (80, 100). IR (KBr): ν (cm^{-1}): 1659 (C=O), 2360 (SH). ^{1}HNMR (DMSO): δ (ppm.): 1.22 (s, 1H, SH), 2.64 (s, 1H, CH_3), 2.73 (s, 3H, SCH_3), 3.30 (s, 1H, CH), 7.00-7.48 (m, aromatic protons + 1H, NH), 9.01 (s, 1H, NH), 10.65 (s, 1H, NH), 11.80 (s, 1H, CHO), Elemental analysis for $C_{19}H_{17}N_5S_3O$ (427.55) Calcd: C, 53.37; H, 4.01; N, 16.38; S, 22.50 Found: C, 53.24; H, 3.89; N, 16.61; S, 22.44.

Synthesis of 4'-(1*H*-indol-3-yl)-6-mercapto-6'-methyl-3',4'-dihydro-[4,5'-bipyrimidine]-2,2'(1*H*, 1'*H*)-dithione (21)

A mixture of compound **5** (0.361 gm, 0.001 mol) and (0.076 gm, 0.001 mol) of thiourea **3b** in (30 ml) ethanol in the presence of sodium ethoxide was heated under reflux for 2 hrs. The solution was concentrated and left to cool; diluted HCl was then added, the product precipitated then it was collected. The yield: 88%, M. P. 250 °C, colour: dark brown, recrystallization from: ethanol/benzene. Mass spectrum m/e (I, %) 385 ($M^{+\cdot}$, 60), (123, 100). IR (KBr): ν (cm^{-1}): 3400 (-NH), 1124 (C=S). ^{1}HNMR (DMSO): δ (ppm.): 2.31 (s, 3H, CH_3), 3.40 (s, 1H, CH), 7.00-7.95 (m, aromatic protons), 9.11 (s, 1H, NH), 9.90 (s, 1H, NH), 11.90 (s, 1H, NH), 12.20 (s, 1H, NH), 13.25 (s, 1H, SH), Elemental analysis for $C_{17}H_{15}N_5S_3$ (385.52) Calcd: C, 52.96; H, 3.92; N, 18.16; S, 24.95 Found: C, 52.96; H, 4.01; N, 18.19; S, 24.79.

Synthesis of (*z*)-3-(hydroxyamino)-1-(2-(hydroxyamino)-6-(1*H*-indol-3-yl)-4-methyl-1,6-dihydropyrimidin-5-yl)-3-mercaptoprop-2-en-1-one hydrochloride (23)

Dithiol **5** (0.361 gm, 0.001 mol) and hydroxyl amine hydrochloride **22** (0.069 gm, 0.001 mol) in (30 ml) ethanol were refluxed for two hrs. The solution was concentrated and left to cool; cold water was then added and the solution was left in the fridge to settle then it was filtered off and the product was collected. The yield: 66%, M. P. 150 °C, colour: dark brown, recrystallization from: ethanol/ benzene. Mass spectrum m/e (I, %) 432 ($M^{+\cdot}$, 10), (66, 100). IR (KBr): ν (cm^{-1}): 3750 (OH), 3223 (NH), 1634 (C=O). ^{1}HNMR (DMSO): δ (ppm.): 0.77-0.0.87 (2s, 2H, NH + SH), 1.23-1.20 (2s, 2H, NH + OH), 2.11 (s, 3H, CH_3), 3.70 (s, 1H, CH), 6.01 (s, 1H, ylidenic CH), 7.06-7.69 (m, aromatic protons + 1H, NH), 11.60 (s, 1H, NH), 13.40 (s, 1H, OH), Elemental analysis for $C_{16}H_{19}Cl_2N_5O_3S$ (432.31) Calcd: C, 44.45; H, 4.43; N, 16.20; S, 7.42; Cl, 16.40 Found: C, 44.57; H, 4.39; N, 16.31; S, 7.42; Cl, 16.52.

Synthesis of cyclic adducts with dithiol 5

General procedures

A mixture of dithiol **5** (0.361 gm, 0.001 mol) and quinones **24-26** (0.001 mol) and/or (0.001 mol) maleic anhydride **27** was heated under reflux in (30 ml) dry xylene for 4 hrs. The reaction mixture was concentrated and it was left aside to cool. The so formed product was collected and recrystallized from the appropriate solvent.

Synthesis of 2-(2-(4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-oxoethylidene)-3*a*,7*a*-dihydrobenzo[*d*][1,3]dithiole-4,7-dione (28)

Obtained from dithiol **5** and *p*-benzoquinone **24**. The yield: 76%, M. P. >300 °C, colour: dark brown, recrystallization from: ethanol/benzene. Mass spectrum m/e (I, %) 467 ($M^{+\cdot}$, 35), (109, 100). IR (KBr): ν (cm^{-1}): 3235 (NH), 1609 (C=O). ^{1}HNMR (DMSO): δ (ppm.): 0.84 (s, 2H, CH-CH), 2.32 (s, 3H, CH_3), 3.40 (s, 1H, CH), 6.56 (s, 1H, ylidenic CH), 6.82-7.89 (m, aromatic protons + CH=CH), 8.40 (1, 1H, NH), 8.61 (s, 1H, NH), 12.20 (s, 1H, NH), Elemental analysis for $C_{22}H_{17}N_3S_3O_3$ (467.57) Calcd: C, 56.51; H, 3.66; N, 8.99; S, 20.57 Found: C, 56.39; H, 3.66; N, 8.72; S, 20.64.

b- Synthesis of 2-(2-(4-(1*H*-indol-3-yl)-6-meth-yl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-

oxoethylidene)-3*a*,9*a*-dihydronaphtho-[2,3-*d*][1,3]dithiole-4,9-dione (29)

Obtained from dithiol **5** and 1,4-naphthoquinone **25**. The yield: 79%, M. P. 230 °C, colour: dark brown, recrystallization from: ethanol/benzene. Mass spectrum m/e (I, %) 517 ($M^{+\cdot}$, 80), (314, 100). IR (KBr): ν (cm^{-1}): 3141 (NH), 1667 (C=O). ^{1}HNMR (DMSO): δ (ppm.): 1.20 (s, 2H, CH-CH), 3.20 (s, 3H, CH_3), 3.31 (s, 1H, CH), 6.99 (s, 1H, ylidenic CH), 7.07-7.89 (m, aromatic protons + 1H, NH), 8.39 (s, 1H, NH), 10.18 (s, 1H, NH), Elemental analysis for $C_{26}H_{19}O_3S_3N_3$ (517.63) Calcd: C, 60.33; H, 3.70; N, 8.12; S, 18.58 Found: C, 60.15; H, 3.33; N, 8.41; S, 18.79.

Synthesis of 2-(2-(4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-oxoethylidene)-3*a*,9*a*-dichloro-3*a*,9*a*-dihydro-naphtho[2,3-*d*][1,3]dithiole-4,9-dione (30)

Obtained from dithiol **5** and 2,3-dichloro-1,4-naphthoquinone **26**. The yield: 79%, M. P. 165 °C, colour: dark brown, recrystallization from: ethanol/benzene. Mass spectrum m/e (I, %) 586 ($M^{+\cdot}$, 25), (191, 100). IR (KBr): ν (cm^{-1}): 3400 (NH), 1681 (C=O). ^{1}HNMR (DMSO): δ (ppm.): 2.60 (s, 3H, CH_3), 4.11 (s, H, CH), 6.81 (s, 1H, ylidenic CH), 7.07-7.91 (m, aromatic protons), 8.10 (s, 1H, NH), 8.24 (s, 1H, NH), 9.99 (s, 1H, NH), Elemental analysis for $C_{26}H_{17}Cl_2O_3N_3S_3$ (586.51) Calcd: C, 53.24; H, 2.92; N, 7.16; S, 16.40; Cl, 12.09 Found: C, 53.53; H, 2.92; N, 7.33; S, 16.22; Cl, 12.27.

Synthesis of 2-(2-(4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-oxoethylidene)dihydro-[1,3]dithiolo[4,5-*c*]furan-4,6-dione (31)

Obtained from dithiol **5** and maleic anhydride **27**. The yield: 81%, M. P. 150 °C, colour: dark brown, recrystallization from: ethanol/benzene. Mass spectrum m/e (I, %) 457 ($M^{+\cdot}$, 30), (246, 100). IR (KBr): ν (cm^{-1}): 3400 (NH), 1716 (C=O). ^{1}HNMR (DMSO): δ (ppm.): 1.56 (s, 2H, CH-CH), 2.40 (s, 3H, CH_3), 4.12 (s, 1H, CH), 6.64 (s, 1H, ylidenic CH), 7.53-7.92 (m, aromatic protons + 1H, NH), 8.41 (s, 1H, NH), 10.70 (s, 1H, NH), Elemental analysis for $C_{20}H_{15}N_3O_4S_3$ (457.50) Calcd: C, 52.50; H, 3.30; N, 9.18; S, 21.02 Found: C, 52.42; H, 3.45; N, 9.22; S, 21.21.

Synthesis of 2-((4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(4-hydroxy-2-(methylthio)benzofuran-3-yl) methylene)cyclohexane-1,3-dione (38)

To a mixture of compound **6** (0.389 gm, 0.001 mol,) and 1,3-cyclohexanedione **32** (0.112 gm, 0.001 mol) in (20 ml) acetonitrile was added (0.1 gm) of aluminium oxide then the mixture was heated under reflux for 6 hrs. The solution was concentrated and left to cool, the product precipitated and then it was collected. The previous reaction was repeated but in this case, marble was used as a base catalyst instead of aluminium oxide; the same results were obtained in all analysis. The yield: 70% in the case of aluminium oxide and 75% in case of marble, M. P. 180 °C, colour: brown, recrystallization from: methanol. Mass spectrum m/e (I, %) 543 ($M^{+\cdot}$, 10), (80, 100). IR (KBr): ν (cm^{-1}): 1600 (C=O), 3396 (OH), 3450 (NH). ^{1}HNMR (DMSO): δ (ppm.): 1.82-2.00 (m, 6H, $3CH_2$), 2.31 (s, 3H, CH_3), 2.73 (s, 3H, SCH_3), 3.30 (s, 1H, CH), 6.83-7.99 (m, aromatic protons + 1H, NH), 9.01 (s, 1H, NH), 10.71 (s, 1H, NH), 11.90 (s, 1H, OH). Elemental analysis for $C_{29}H_{25}O_4S_2N_3$ (543.63) Calcd: C, 64.07; H, 4.63; N, 7.73; S, 11.80 Found: C, 64.13; H, 4.54; N, 7.99; S, 11.62.

Synthesis of 4-(1*H*-indol-3-yl)-6-methyl-5-(3-thioxo-3*H*-1,2-dithiol-5-yl)-3,4-dihydropyrimidine-2(1*H*)-thione (39)

To the dithiol **5** (0.361 gm, 0.001 mol) in dry benzene was added phosphorus pentasulfide (0.222 gm, 0.001 mol). The reaction mixture was heated on a water bath for 5 hrs, and then it was filtered while hot, the clear benzene layer was concentrated to its half volume followed by addition of appropriate quantity of petroleum ether 40/60. The precipitated solid product was filtered off and washed twice with petroleum ether 40/60 giving the required thione **39**. The yield: 30%, M. P. 110 °C, coulor: brown, recrystallization from: benzene. Mass spectrum m/e (I, %) 375 ($M^{+\cdot}$, 20), (75, 100). IR (KBr): ν (cm^{-1}): 1237 (C=S), 3230 (NH). ^{1}HNMR (DMSO): δ (ppm.): 2.14 (s, 3H, CH_3), 3.60 (s, 1H, CH), 6.05 (s, 1H, ylidenic CH), 6.92-7.78 (m, aromatic protons), 8.19 (s, 1H, NH), 8.83 (s, 1H, NH), 11.58 (s, 1H, NH). Elemental analysis for $C_{16}H_{13}S_4N_3$ (375.31) Calcd: C, 51.20; H, 3.49; N, 11.20; S, 34.10 Found: C, 51.41; H, 3.17; N, 11.32; S, 34.45.

Synthesis of (*z*)-5-(1,2-dimercaptovinyl)-4-(1*H*-indol-3-yl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione (41)

A mixture of dihydropyrimidine **4b** (0.285 gm, 0.001 mol), (0.222 gm, 0.001 mol) of phosphorous pentasulfide and (0.256 gm, 0.001 mol) of the elemental sulfur in (30 ml) DMF was heated under reflux for 6 hrs. The mixture was filtered while hot. The clear DMF was concentrated to its half volume

followed by addition of appropriate quantity of cold water to precipitate the solid product. The mixture was left aside to cool. After complete precipitation the solution was filtered off and the precipitate was collected. The yield: 88%, M. P. >300 ^{o}C, colour: dark brown, recrystallization from: DMF. Mass spectrum m/e (I, %) 333 ($M^{+\cdot}$, 30), (73, 100). IR (KBr): ν (cm^{-1}): 2362 (SH), 2917 (SH), 3230 (NH), 1237 (C=S). ^{1}HNMR (DMSO): δ (ppm.): 2.73 (s, 3H, CH_3), 2.88 (s, 2H, 2SH), 3.32 (s, 1H, CH), 6.10 (s, 1H, ylidenic CH), 7.05-7.45 (m, aromatic protons + 1H, NH), 7.95 (s, 1H, NH), 11.00 (s, 1H, NH), Elemental analysis for $C_{15}H_{15}N_3S_3$ (333.49) Calcd: C, 54.02; H, 4.53; N, 12.60; S, 28.85 Found: C, 54.40; H, 4.31; N, 12.11; S, 28.93.

Synthesis of 3-(4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-8*a*-mercapto-6,7-dihydro-8*aH*-[1,2]dithiolo[3,4-*b*]benzofuran-4(5*H*)-one (43)

To a mixture of compound **39** (0.375 gm, 0.001 mol) and 1,3-cyclohexanedione **32** (0.112 gm, 0.001 mol) in (20 ml) acetonitrile was added (0.1 gm) of marble, the mixture was heated under reflux for 6 hrs. The solution was concentrated and left to cool. The product precipitated and then it was collected. The yield; 75%, M. P. 170 ^{o}C, colour: brown, recrystallization from: benzene. Mass spectrum m/e (I, %) 485 ($M^{+\cdot}$, 30), (64, 100). IR (KBr): ν(cm^{-1}): 1620 (C=O), 2359 (SH), 3408 (NH). ^{1}HNMR (DMSO): δ (ppm.): 1.23-1.40 (m, 6H, $3CH_2$), 2.00 (s, 1H, SH), 2.21 (s, 3H, CH_3), 3.32 (s, 1H, CH), 6.80-7.78 (m, aromatic protons), 8.80 (s, 1H, NH), 10.01 (s, 1H, NH), 11.43 (s, 1H, NH), Elemental analysis for $C_{22}H_{19}N_3O_2S_4$ (485.62) Calcd: C, 54.41; H, 3.94; N, 8.65; S, 26.41 Found: C, 54.17; H, 4.13; N, 8.33; S, 26.57.

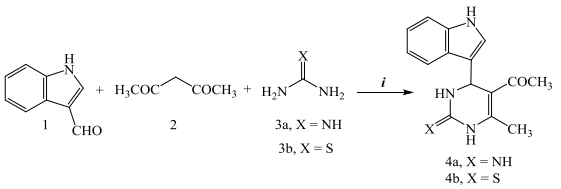
Synthesis of 5,5'-((1z,4z)-1-hydroxy-3,3-bis(methylthio)-5-morpholinopenta-1,4-diene-1,5-diyl)bis(4-(1*H*-indol-3-yl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione) (47)

To a mixture of compound **45** (0.354 gm, 0.001 mol) and compound **6** (0.389 gm, 0.001 mol) in (20 ml) benzene was added (0.1 gm) marble. This mixture was heated under reflux for 6 hrs. The solution was concentrated and left to cool, the product precipitated and then it was collected. The yield: 70%, M. P. >300 ^{o}C, colour: dark brown, recrystallization from: methanol. Mass spectrum m/e (I, %) 743 ($M^{+\cdot}$, 67), (432, 100). IR (KBr): ν (cm^{-1}): 3267 (NH), 3408 (NH), 3450 (OH). ^{1}HNMR (DMSO): δ (ppm.): 1.20 (s, 1H, OH), 2.30 (s, 6H, $2CH_3$), 2.73 (s, 6H, $2SCH_3$), 2.89 (s, 4H, $2CH_2$), 3.21 (s, 2H, $2CH_2$) 4.01 (s, 2H, 2CH), 6.01 (s, 2H, ylidenic 2CH), 6.84-7.48 (m, aromatic protons), 8.00 (s, 2H, 2NH), 9.01 (s, 2H, 2NH), 10.00 (s, 2H, 2NH), Elemental analysis for $C_{37}H_{41}N_7O_2S_4$ (743.22) Calcd: C, 59.73; H, 5.55; N, 13.18; S, 17.24 Found: C, 59.92; H, 5.20; N, 13.47; S, 17.35.

3. Results and discussion

It is well known that dihydropyrimidines are heterocycles, have aroused interest in medicinal chemistry due to alleged versatile biological activity. Furthermore the naturally occurring indole explored heterocyclic ring systems with wide range of applications in pathophysiological conditions. Moreover dithiolthiones also exhibit more potent therapeutic activity especially as anticancer agents e.g. oliptraz. Owing to the forgoing information we could build a molecule contained the three nuclei in the hope of obtaining a more potent products.[29,30]

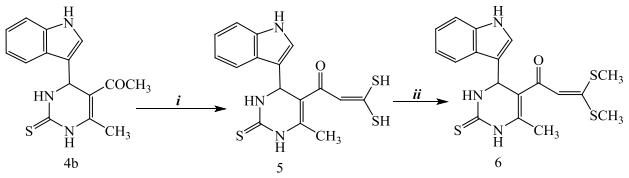
Here in we used pure orange juice as a solvent and as an acid catalyst for synthesizing the starting material; dihydropyrimidine derivatives [5,31] **4a** and **4b** via a one pot three components reaction of 3-indole aldehyde **1**, acetylacetone **2** and urea **3a** and/or thiourea **3b** Scheme 1.



Scheme 1 Synthesis of 4a and 4b
Reagents and conditions ***i*** pure orange juice/Reflux 2-4h

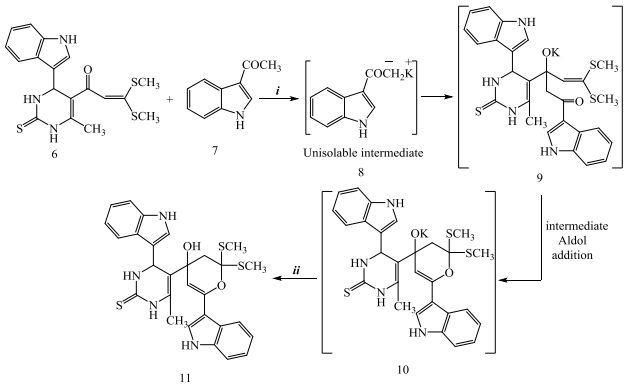
The substrates **4a** and **4b** which contain both dihydropyrimidine and indole nucleus were used as key synthons for synthesizing of α-oxoketene *gem*-dithiol [26] which has been used in organic synthesis especially in the synthesis of various aromatic and heterocyclic compounds.

On developing the chemistry of **4b** it was treated with carbon disulphide in the presence of K.*tert*. butoxide and gave the oxoketene *gem*-dithiol derivative **5**. Subsequently methylation of **5** with methyl iodide gathered the ketene diothioacetals **6** Scheme 2.



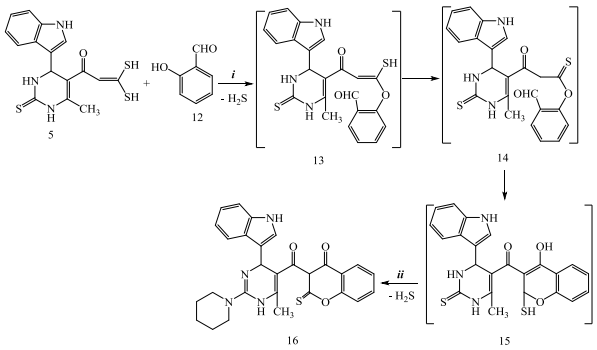
Scheme 2 Synthesis of 5 and 6
Reagents and conditions ***i*** CS_2/K. *ter*. BuO/benzene/ice bath, stirring, ***ii*** CH_3I/ice bath, stirring 4h

Oxoketene *gem*-dithioacetal **6** reacts with 3-acetylindole **7** in the presence of KOH in DMSO to give pyrane derivative **11** Scheme 3.



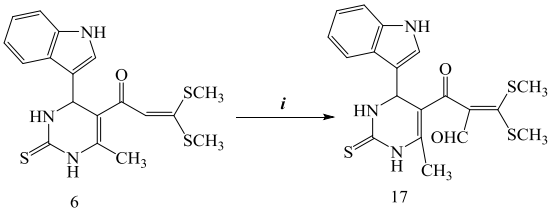
Scheme 3 Synthesis of 11
Reagents and conditions ***i*** KOH/DMSO/stirring/10-15 °C/6h, ***ii*** cold diluted HCl

In the synthetic application by base catalyzed reaction of oxoketene *gem*-dithiol; we have reacted oxoketene *gem*-dithiols **5** with salicyaldehyde **12** in THF and piperidine as a basic catalyst to offer a facile, convenient, efficient and reasonable yield. The suggested synthetic route for formation of 3-aroylcoumarine **16** is assumed to proceed *via* Michael addition prior to Kneovenagel's condensation and then intermolecular cycloaddition Scheme 4.



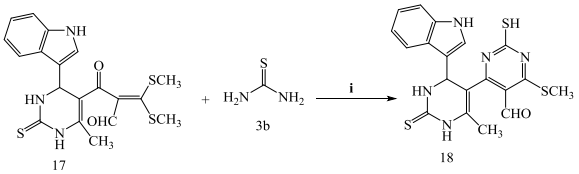
Scheme 4 Synthesis of 16
Reagents and conditions ***i*** THF/piperidine/Reflux 6h, ***ii*** piperidine

A new trend in the chemistry of oxoketene *gem*-dithiol and due to electronic rich character of α-carbon in oxoketene *gem*-dithioacetal, it is quite reactive to Vilsmeier's [32] reagent. In the present work, formylation of ketene diothioacetals **6** with $POCl_3$/DMF was performed to give the formylated adduct **17** with the aim to develop new α-functionalization and cyclization reactions Scheme 5.



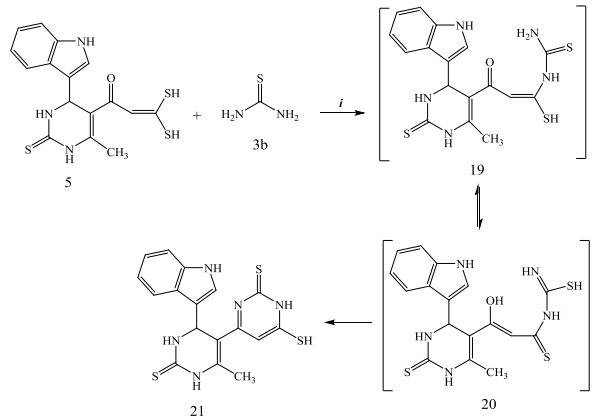
Scheme 5 Synthesis of 17
Reagents and conditions ***i*** $POCl_3$/DMF/ice bath/stirring 2h/ aq. K_2CO_3

The synthetic utility of α-formyl ketene dithioacetal **17** was explored by synthesis of the substituted bipyrimidine derivative **18** by condensation of thiourea **3b** in acetonitrile and potassium carbonate with **1**7 which showed that it was the keto group condensation in the substrate **17** instead of the formyl group, that took a part in the reaction, hence resulting in the formation of bipyrimidine derivative **18** Scheme 6.



Scheme 6 Synthesis of 18
Reagents and conditions ***i*** K_2CO_3/CH_3CN/Reflux 4h

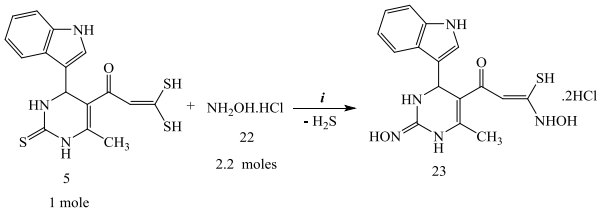
Moreover, treating the oxoketene *gem*-dithol **5** with thiourea **3b** in ethanol and sodium ethoxide, led to the addition of thiourea to β-carbon followed by dehydration to form bipyrimidine derivative **21** Scheme 7.



Scheme 7 Synthesis of 21
Reagents and conditions ***i*** C_2H_5OH/C_2H_5ONa/Reflux 2h

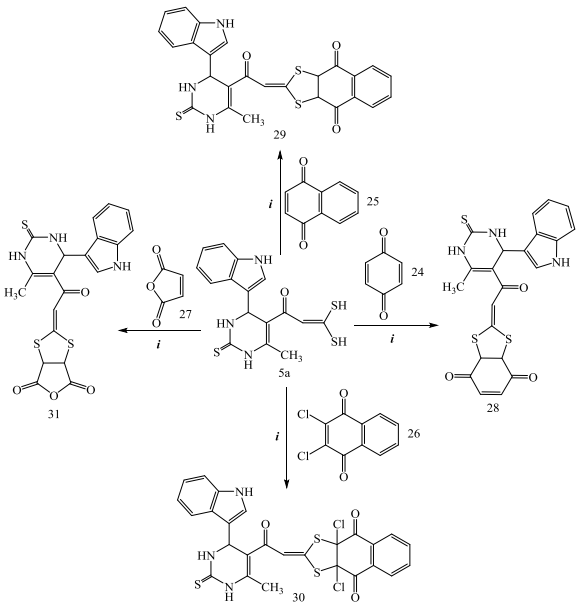
Reaction of oxoketene *gem*-dithiol with hydroxylamine hydrochloride in an equimolar ratio in both acid and in base media was earlier reported [33]. Herein we reported on the reaction of hydroxylamine hydrochloride **22** (2.2 moles) with oxoketene *gem*-dithiol **5** (1 mole) in ethanol under reflux. It was noticed that replacement of sulfohydryl functional

group by hydroxylamine hydrochloride **22** is superior and finally **23** was collected Scheme 8.



Scheme 8 Synthesis of 23
Reagents and conditions ***i*** C_2H_5OH/Reflux 2h

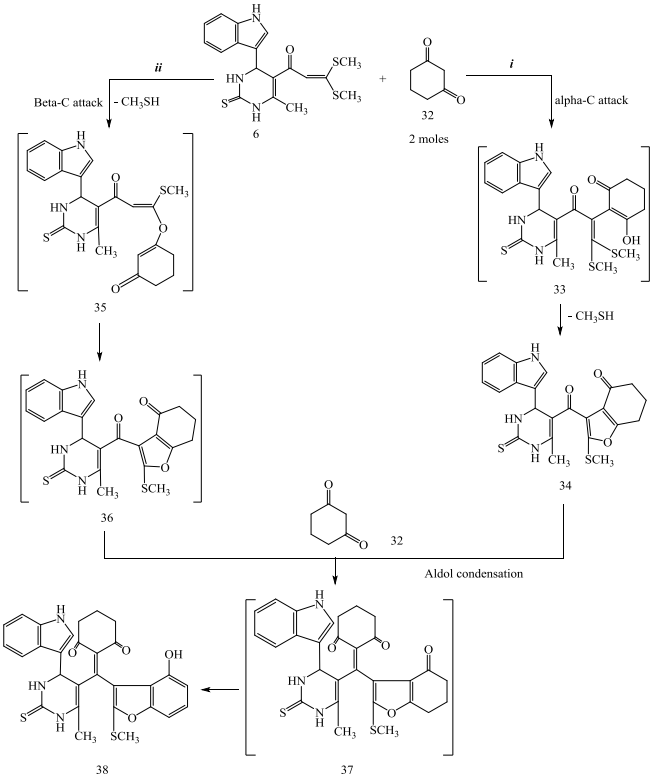
On treating oxoketene *gem*-dithiol **5** with some quinones **24-26** e.g. *p*-benzoquinone, naphthoquinone and 1,4-dichloronaphthaquinone and/or with maleic anhydride **27**, the reaction products **28-31** were obtained. Formation of **28-31** is proposed to proceed through (3 + 2) cycloaddition reaction [26] Scheme 9.



Scheme 9 Synthesis of 28-31
Reagents and conditions ***i*** dry xylene/Reflux 4h

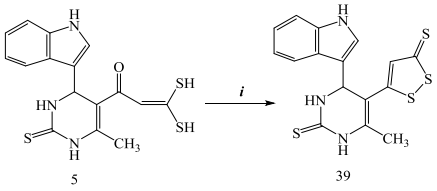
Convenient and facile transformation processes of oxoketene *gem*-dithioacetal **6** to methyl thiobenzofuran derivative **38** could be achieved through the reaction of **6** (1 mole) with 1,3-cyclohexanedione **32** (2 moles) in both acid and base catalysts. Formation of **38** in Al_2O_3 as an acid catalyzed reaction is assumed to proceed via acid catalyzed alkylation, through addition to α-carbon followed by enolic addition to β-carbon, then intramolecular cyclization and finally the second molecule of 1,3-cyclohexanedione condenses with carbocation to give methyl thiobenzofuran **38**. Meanwhile the same molar ratio of **6** and **32** was taken in the presence of marble as a basic catalyst, which also proved to be an efficient catalyst for transformation of **6** to methyl thiobenzofuran derivative **38**.

The base catalyst, marble activates electrophilic addition of enolic form of 1,3- cyclohexanedione **32** to β-carbon in **6**, followed by Michael addition to α-carbon then, the second molecule of 1,3-cyclohexanedione **32** condenses with keto group to form **38** Scheme 10.



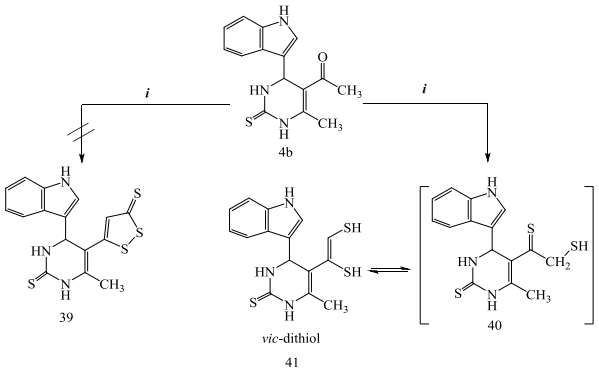
Scheme 10 Synthesis of 38
Reagents and conditions ***i*** CH_3CN/Al_2O_3 (acid cat.)/Reflux 6h, ***ii*** CH_3CN/marble (base cat.)/ Reflux 6h

Extension to our work on *gem*-dithiol **5**, we reacted **5** with P_2S_5 in dry benzene; 1,2-dithiol-3-thione derivative **39** was obtained in a moderate yield [26] Scheme 11.



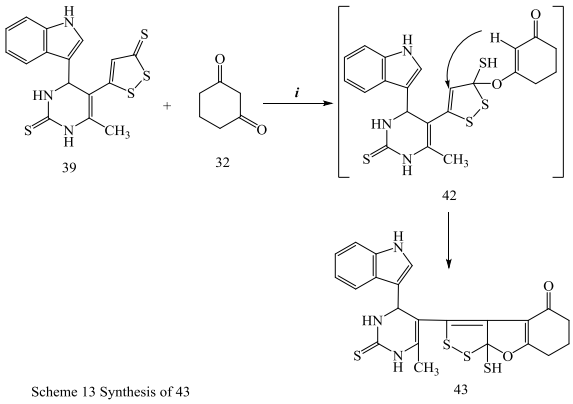
Scheme 11 Synthesis of 39
Reagents and conditions ***i*** dry benzene/P_2S_5/Reflux 5h/water bath

Moreover, sulfurization of **4b** with P_2S_5 and in the presence of elemental sulfur in DMF while reflux; *vic*-dithiol **41** was gathered instead of the expected 1,2-dithiol-3-thione **39** Scheme 12.



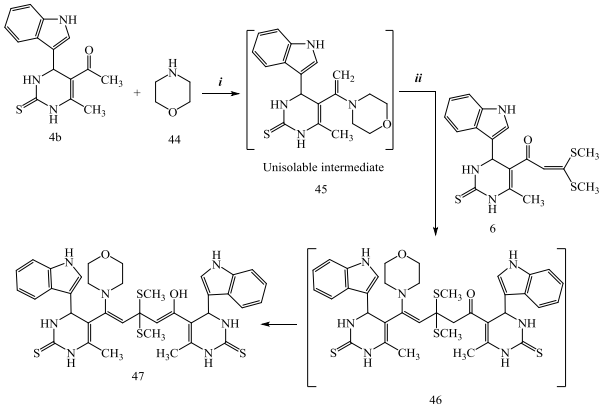
Scheme 12 Synthesis of 41
Reagents and conditions ***i*** DMF/P_2S_5/S_8/Reflux 6h

Herein we carried out a new trend for exploring the chemistry of 1,2-dithiol-3-thione **39** towards 1,3-diketones **32**. Thus when **39** was treated with 1,3-cyclohexanedione **32** in the presence of marble as a base catalyst in boiling acetonitrile afforded furan derivative **43** in a satisfactory yield Scheme 13.



Scheme 13 Synthesis of 43
Reagents and conditions ***i*** CH_3CN/marble/Reflux 6h

A new C-C bond formation involving induced addition of **45** (which could easily be prepared from acetyl pyrimidine via its reaction with morpholine in boiling benzene) with α-oxoketene dithioacetal **6** under the effect of marble as a base catalyzed reaction in refluxing benzene resulted in the formation of **47** Scheme 14.



Scheme 14 Synthesis of 47
Reagents and conditions ***i*** benzene/Reflux 4h, ***ii*** benzene/marble/Reflux 6h

4. Antimicrobial activity

Several bioassays such as disk-diffusion, well diffusion and broth or agar dilution are well known and commonly used in this test; small filter paper disks (6 mm) impregnated with a standard amount of antibiotic is placed onto an agar plate to which bacteria has been swabbed. The plates are incubated over night and the zone of inhibition of bacterial growth is used as a measure of susceptibility. Antimicrobial activity of the tested samples was determined using a modified Kirby-Bauer disc diffusion method.[34-36]

Title products were in vitro examined against Gram positive and Gram negative bacteria and against fungi e.g. (Escherichia Coli Staphylo-coccus aureus (G+), Aspergillus flavus (Fungus), and Candida albicans (Fungus) in comparison with Ampicillin: antibacterial agent and Amphotericin B: antifungal agent. The examined compounds are: 4a, 5, 11, 16 -18, 21, 23, 28-30, 38, 39 and 47. Most of the synthesized products exhibited moderate antimicrobial activity. The inhibition zones were expressed in numbers comparing with those of Ampicillin antibacterial and Amphotericin B.

Table 1: Bactericidal and fungicidal activity of some of the newly prepared compounds

Sample	Inhibition zone diameter (mm/mg Sample)			
	Escherichia Coli (G)	Staphylococcus aureus (G^+)	Aspergillus flavus (Fungus)	Candida albicans (Fungus)
Control: DMSO	0.0	0.0	0.0	0.0
Ampicillin: Antibacterial agent	30	24	--	--
Amphotericin B: Antifungal agent	--	--	16	19
4a	16	14	0.0	12
5	16	14	0.0	0.0
6	12	13	0.0	0.0
11	15	13	0.0	0.0
16	13	13	0.0	0.0
17	14	12	0.0	0.0
18	14	14	0.0	0.0
21	14	14	0.0	0.0
23	14	14	0.0	0.0
28	14	14	0.0	12
29	16	16	16	20
30	13	13	0.0	0.0
38	14	13	0.0	0.0
39	15	15	0.0	14
47	14	14	0.0	0.0

5. Conclusions

In summary we have discussed the synthesis of some indolyldihydropyrimidines contained oxoketene dithiols, ketenedithioacetal and /or 1,2-dithiol 3-thione derivatives using green condition; pure orange juice which acts as solvent and acid catalyst. All newly synthesized compounds have been fully characterized. Furthermore, all the new indolyldihydropyrimidines contained oxoketene, dithiols, ketene dithioacetals and /or 1,2-dithiol 3-thione derivatives were evaluated for their antimicrobial activity. The study revealed that some of the prepared products exhibit antibacterial and antifungal activities, compared to that of the reference known drugs Ampicilline and Amphotricin.

6. Conflicts of interest

The authors would like to clear that, they have no conflicts of interest in publication of this paper in Egyptian Journal of Chemistry.

7. Acknowledgments

The authors would like to thank Micro analytical center and Microbiology lab. at Cairo University .

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داي هيدروبيرميدين كركائز في تخليق اوكسوكيتين جيم دايثيول و ١و٢ - داي ثيول -٣- ثيون ، تخليق سهل و تفاعلات مناسبة

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أمكن تحضير مشتقات الداي هيدروبيردين من تفاعل الاندول الدهيد ١ مع الاستيل اسيتون ٢ و مشتقات اليوريا ٣أو ٣ب في وسط حامضي من عصير البرتقال الخالص و قد حصلنا علي مركبات الدي هيدروبيرميدين ٤أ و ٤ب و التي بدورها استخدمت في تحضير مركبات الداي ثيول ٥ و الاسيتال ٦. و عندما تم معاملة الاسيتال ٦ بمركب ٣ - اسيتايل اندول ٧حصلنا على مشتق البيران ١١. كذلك عند تفاعل المركب ٥ مع ساليسالدهيد ١٢ حصلنا ايضا على الكومارين ١٦. عند اجراء تفاعل فيلزماير على الاسيتال ٦ أعطي مشتق الفورمايل ١٧و الذي بدوره عند تفاعله مع الثيويوريا ٣ب أعطى الداي بيرميدين ١٨. و قد حصلنا ايضا على مركب الداي بيرميدين ٢١ بتفاعل الدي ثيول ٥ مع الثيويوريا ٣ب. عند تفاعل المركب ٥ مع الهيدروكسيل أمين هيدروكلوريد ٢٢حدث استبدال لمجموعات السلفاهيدريل لينتج المركب ٢٣. يتفاعل المركب ٥ مع الكينونات٢٤-٢٦ و كذلك مالييك انهيدريد ٢٧ لينتج مركبات ٢٨-٣١. يتفاعل الاسيتال ٦ مع السيكلوهكسان دايون ٣٢ في وجود عامل حفاز حمضي من اكسيد الالومنيوم و كذلك في وجود عمل حفاز قاعدي من الماربل لنحصل على نفس المركب و هو مشتق البنزوفيوران ٣٨. عند تفاعل الداي ثيول ٥ مع خامس كبريتيد الفسفور أعطي مركب ١و٢ - داي ثيول -٣- ثيون ٣٩. عند تفاعل اسيتايل داي هيدروبيرميدين ٤ب مع خامس كبريتيد الفسفور و الكبريت العنصري حصلنا على مركب فيك داي ثيول ٤١ على خلاف المتوقع حيث اننا كنا نتوقع الحصول على المركب ٣٩. عند تفاعل المركب ٣٩ مع السيكلوهكسان دايون ٣٢ حصلنا على مشتق الفيوران ٤٣. كما تفاعل مشتق الدي هيدروبيرميدين ٤٥ مع الاسيتال ٦ و نتج مركب البيس داي هيدروبيرميدين ٤٧. و قد تم اثبات تركيب هذه المركبات الجديدة عن طريق اجراء تقدير للعناصر و كذلك التحاليل الطيفية كتقدير الكتلة و الرنين النووي المغناطيسي و الاشعة تحت الحمراء. أيضاً تم عمل دراسة بيولوجية لمعرفة مدى تأثير المركبات التي تم تحضيرها مقارنة بالامبسللين و الامفترسين ب على بعض الكائنات الدقيقة و قد أعطى بعضها نتائج مُرضية.