Synthesis and Invitro study of 4-(indolyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate Derivatives Promoted Natural acids

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ABSTRACT:

In the current study, a novel 4-(indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl) ethanone was synthesized from a mixture of substituted indole-3-carbaldehydes (1.150 mol), 1,3-diketones like acetyl acetone (1 mol), and thiourea (2 mol) at room temperature. Advanced spectroscopic data such as ^{1}HNMR, ^{13}C NMR, & LCMS were used to analyze newly synthesized compounds, and elemental analysis was used to derive the structural determination. Additionally, the microbiological activity of each freshly synthesized molecule was assessed.

KEYWORDS:

Acetylacetone, indole-3-carbaldehydes, natural lemon juice, Tetra hydro pyrimidines -2 -thiones, biological activity

1. INTRODUCTION:

In both chemical and medicinal chemistry, the synthesis of 2-thioxo-1,2,3,4-tetrahydropyrimidines is a significant and fascinating process. In organic synthesis, this moiety is a crucial intermediary. The pyrimidine-2-thione fragment can be found in a number of medicinal and physiologically active compounds [1-3]. As a result, pyrimidine analogs and their hydrogenation products have received increased attention. Numerous biological and pharmacological properties, including antidepressant [4], calcium antagonist [5,6], anticancer [7], antitubercular [8], anti-inflammatory [9,10], antibacterial and antifungal effects [11,12], analgesic [13,14], antioxidant [15], etc., are present in this class of moieties.

These days, the most widely used one-step procedures in synthetic organic chemistry for the synthesis of heterocyclic compounds use three reactants condensed with a variety of reagents and catalysts. Due to their shorter reaction times, ease of product isolation, and greater yields and recoveries of the by-product, these one-step procedures are more practical than multi-step ones [16–18]. The synthesis of indole-3-carbaldehyde, acetyl acetone, thiourea, and silica sulfuric acid as a Bronsted acid catalyst, as well as the utilization of solvent systems at room temperature, are all part of our comprehensive investigation to develop and synthesize new pyrimidine-2-thiones derivatives in the current work. The several indole aldehydes used to prepare the named equivalent

2. METHODS AND MATERIALS:

2.1. EXPERIMENTAL;

Fine Chemicals supplied all of the chemicals, solvents, and synthetic grade reagents that were employed without any additional purification. Thin layer chromatography was used to track the reaction's development (EtOAc: n-hexane = 4:65). Using an Electrochemical Mk3 equipment, the melting point of each newly synthesized derivative was measured open at one end and left uncorrected. The 400MHz Brucker spectrometer was used to record the 1HNMR and 13CNMR spectra in CDCl3 as a solvent. The chemical shift values were recorded in units δ (ppm) in relation to tetramethylsilane (Me4Si) as an internal standard. The LCMS spectrometer was used to determine the molecular mass of the produced molecule. Elemental analysis can be used to determine the compounds' structures.

2.2. GENERAL PROCEDURE FOR SYNTHESIS TITLED DERIVATIVES:

In a 50 ml RB flask, a combination of substituted indole-3-carbaldehyde (1 mol), acetyl acetone (1 mol), and thiourea (2 mol) is added. The mixture was progressively dissolved by adding an acid catalyst, such as 4 milliliters of natural lemon juice. The magnetic stirrer was used to conduct the reaction mixture at room temperature. TLC in ethyl acetate:n-hexane (4:6) was used to monitor the reaction's development.Once the reaction was finished, the mixture was allowed to cool to room temperature before being added to 100 milliliters of broken ice. Ethyl acetate and a saturated sodium bicarbonate solution were used to filter and wash the crude three times. Column chromatography (Ethyl acetate: n-hexane, 4:6) can be used to separate the solid product, as shown in Scheme I.

Characterization:

1)1-(4-(1H-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)ethanone (4a):

Paleredcompound;yield-86%;m.p–169-171^{0}c,^{1}HNMR(400MHz,$CDCl_3$)δppm:10.195 (s,1H, N-H(indole)),9.414(s,1H,N-H(pyrimidine)),9.125(s,1H,N-H(pyrimidine)),7.426(d,J=7.6Hz, 1H,Ar-H),7.118(d,J=8.4Hz,Ar-H),7.057(s,1H,Indole),4.628(s,1H,4(H)),2.168(s,3H,-$COCH_3$), 1.452(s,3H, -CH_3). ^{13}CNMR (100MHz, $CDCl_3$) δ in ppm: 193.87, 185.41, 148.88, and 142.95, LCMS (m/z):384.54. Molecularformule: $C_{21}H_{24}N_2O_5$; Elemental analysis: Calculated: C-65.62, H-6.29, N-7.28. Obtained: 65.56, H-6.27, N-7.35.

2).1-(4-(5-methoxy-1H-indol-3-yl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl) ethanone (4b):

Paleredcompound:Yield-92%;m.p–206-208^{0}c;^{1}HNMR(400MHz,$CDCl_3$)δppm:.10.257(s,1H, N-H(indole)),9.366(s,1H,N-H(pyrimidine)),8.985(s,1H,N-H(pyrimidine)),7.374(d,J=9.6Hz, 1H,Ar-H),7.175(s,1H,Indole),7.065(d,J=8.0Hz,Ar-H),4.513(s,1H,4(H)),1.976(s,3H,-$COCH_3$), 0.948(s,3H,-CH_3).^{13}CNMR(100MHz,$CDCl_3$)δinppm:193.48,184.65,148.58,141.45,129.06, 128.84,128.24,127.23,126.67,125.41,123.95,121.04,112.22,55.71,50.76,26.74,18.26.LCMS (m/z):316.54(M+H).Molecularformula:$C_{16}H_{17}N_3O_2S$.Elementalanalysis:calculated:C-60.92, H-5.43, N-13.31. Obtained: C-60.87, H-5.41, and N-13.38

3).1-(4-(5-fluro-1H-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) ethanone (4c):

Paleredcompound;Yield-88%;m.p–171-173^{0}c.^{1}HNMR(400MHz,$CDCl_3$)δppm:10.478(s,1H, N-H(indole)),9.514(s,1H,N-H(pyrimidine)),9.145(s,1H,N-H(pyrimidine)),7.627-7.487(m,3H ,Ar-H),7.231(s,1H,Ar-H),4.487(s,1H,4(H)),2.502(s,3H,-$COCH_3$),1.612(s,3H,-CH_3).^{13}CNMR (100MHz,$CDCl_3$)δppm:194.77,188.48,148.56,136.67,129.76,128.52,127.04,126.12,125.95, 124.66,122.34,121.58,109.71,52.16,26.75,19.21.LCMS(m/z):305.65(M+2).Molecular formula: $C_{15}H_{14}FN_3OS$. Elemental analysis: Calculated: C-59.38, H-4.65, N-6.27. Obtained: C-59.31, H-4.64, N-6.35.

3).1-(4-(5-fluro-1H-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) ethenone (4d):

Redcompound;Yield-89%;m.p–189-191^{0}c.^{1}HNMR(400MHz,$CDCl_3$) δ ppm :10.567 (s,1H, N-H), 9.658 (s, 1H, N-H), 9.235 (s, 1H, N-H), 7.636-7.427(m, 3H ,Ar-H), 7.231(s,1H,Ar-H),4.487(s,1H,C-$_4$), 2.515 (s, 3H, -$COCH_3$) , 1.658 (s, 3H, -CH_3) .^{13}CNMR (100MHz, $CDCl_3$) δ ppm : 194.77, 188.48, 148.56, 136.67, 129.76, 128.52, 127.04, 126.12, 125.95, 124.66, 122.34, 121.58, 109.71, 52.16, 26.75, 19.21 .LCMS (m/z) : 305.65(M+2) .Molecular formula : $C_{15}H_{14}FN_3OS$. Elemental analysis: Calculated: C-59.38, H-4.65, N-6.27. Obtained: C-59.31, H-4.64, N-6.35.

4).1-(4-(5-bromo-1H-indol-3-yl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-yl) ethanone (4e):

Pale red solid; Yield-87%; M.p – 201-203^{0}c :^{1}HNMR (400MHz, $CDCl_3$) δ ppm : 10.745 (s, 1H, -NH), 9.587 (s, 1H, NH Pyrimidine), 9.345 (s, 1H, NH pyridine), 7.589 (d, J=8.8Hz, 1H, Ar-H), 7.484 (d, J=8.9Hz, 1H, Ar-H), 7.294 (s, 1H, Ar-H), 7.114 (d, J=7.2Hz, 1H, Ar-H), 4.358 (s, 1H, -CH-), 2.358 (s, 3H, -$COCH_3$), 2.075-1.845 (m, 2H, Ar-H) .^{13}CNMR (100MHz, $CDCl_3$) δ in ppm: 197.19, 188.95, 145.58, 133.71, 128.48, 127.12, 125.05, 123.39, 121.74, 119.28, 117.84, 106.47, 51.38, 28.40, 19.65. LCMS (m/z): 365.58(M+1). Molecular formula: $C_{15}H_{14}BrN_3OS$. Elemental analysis: Calculated: C-49.48, H-3.86, N-11.58, Obtained: C-49.42, H-3.84, N-11.65.

5).3-(5-acetyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)-1H-indole-5-carbonitrile (4f):

Pale pink-solid; yield-87%; M.p –215-217^{0}c ,^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 10.598 (s,1H,N-H), 9.808 (s, 1H, N-H), 9.319 (s, 1H, N-H), 7.587 - 7.458 (m, 3H, Ar-H), 7.347 (s,1H,Indole),4.441 (s,1H, 4(H)),2.156(s,3H,-$COCH_3$),1.901(s,3H,-CH_3). ^{13}CNMR (100MHz, $CDCl_3$) δ in ppm: 194.58, 188.05, 151.33, 129.49, 128.05, 125.74, 124.04, 122.17, 121.16, 118.33, 112.74, 108.59, 51.11, and 26.72,17. 65. LCMS (m/z):310.46. Molecular formula:

$C_{16}H_{14}N_4OS$. Elemental analysis: calculated: C-61.90, H-4.55, N-18.06. Obtained: C-61.84, H-4.54, N-18.14.

6).1-(6-methyl-4-(5-nitro-1H-indol-3-yl)-2-thixo-1,2,3,4-tetrahydropyrimidin-5-yl) ethenone (4g):

Yellowpoder;Yield-85%; M.p–224-226^{0}c: ^{1}HNMR (400MHz, $CDCl_3$)δ ppm : 10.847 (s, 1H, N-H), 9.884 (s, 1H, N-H)), 9.258 (s, 1H, N-H), 7.784 (d, J=8.0Hz, 1H, Ar-H), 7.378 (d, J=8.8Hz, Ar-H), 7.317 (s, 1H, Indole), 4.678 (s, 1H, C-4), 2.741 (s, 3H, -$COCH_3$) , 1.746 (s, 3H, -CH_3). ^{13}CNMR (100MHz, $CDCl_3$) δppm: 194.25, 187.15, 147.87, 138.87, 132.79, 128.74, 127.44, 125.58, 124.78, 121.28, 119.78, 112.54, 109.86, 53.77, 27.54, 20.14. LCMS(m/z): 330.78. Molecular formula$C_{15}H_{14}N_4O_3S$. Elemental analysis: calculated: C-54.54, H-4.27, and N-16.98. Obtained: C-54.46, H-4.26, N-17.10.

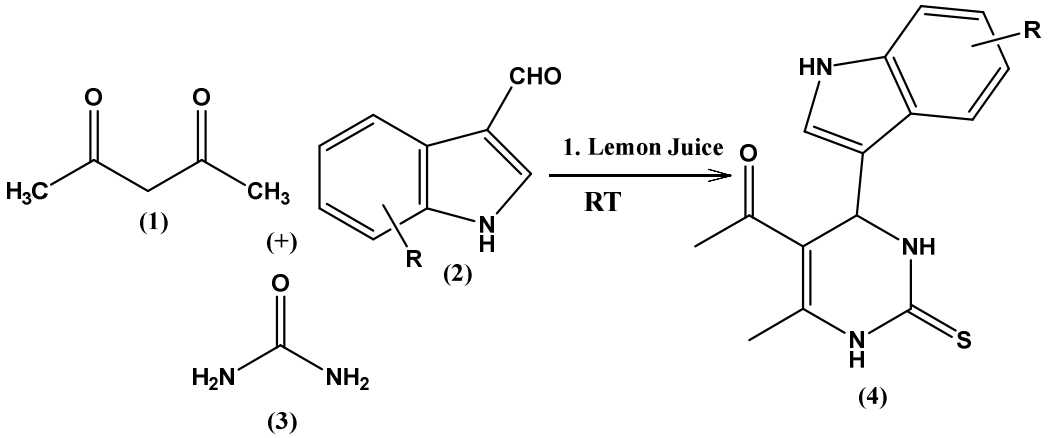
3. BIOLOGICAL ACTIVITY:

Anti- Fungal Activity:

The ***Invitro*** anti-fungal activities of new prepared compounds were examined by disc diffusion method against the organism of Aspergillus Niger and Candida albicans. The target compounds were used at the various concentration and average value and using DMSO as a solvent. The standard drug was used as ketoconazole 50 µglml against both organisms.

4. RESULT & DISCUSSION:

4.1. Chemistry:



R = H, 5-OMe, 5-F, 5-Br, 5-$COCH_3$, 5-NO_2

(Scheme-1)

Initially, the target molecules can be synthesized from the reaction of substituted indole -3-carbaldehydes (1.150 mol), acetyl acetone (1mol), thiourea (2mol) in the presence of new catalyst natural lemon juice at RT conditions. All prepared derivatives were synthesized under at RT condition. These target derivatives were obtained. The advantages of these catalysts can be used to accelerate the rate of reaction and reaction is completed maximum two hours. The rate of reaction enhanced by using these catalysts Silica sulphuric acids

catalyst. We used various substituted indole -3-carbaldehyde having electron donating group of indoles -3- carbaldehyde and electron attracting group of indoles -3- carbaldehyde aldehydes and halogen containing indole -3-carbaldehyde aldehydes.

4.2. BIOLOGICAL ACTIVITY:

All the desired compounds were evaluated by ***invitro*** anti-antifungal activity. The electron withdrawing group of compounds and electron releasing group compounds were showed the various potent activities. Therefore, electron withdrawing group of compounds exhibited poor biological potent activity compared with electron donating groups. All halogen compounds showed an excellent activity. The compound which possesses electron donating group showed moderate activity as shown in Table-I.

Table-I: Antimicrobial activity screening activity synthesized scaffold:

Compound Code	Fungi	
	A. Niger	C. albicans
4a	07	08
4b	11	09
4c	16	14
4d	16	18
4e	14	11
4f	09	08
4g	12	13
Streptomycin	NA	NA
Ketoconazole	20	20
DMSO	---	---

5. CONCLUSION:

The reaction condition was maintained at RT condition for all the newly titled derivatives. The yields of the desired compounds were prepared from 84-92%. This compound contained electron donating group acquired maximum high yield than that of the compound were containg electron attracting group. The rates of the reaction of the desired compounds are developed by using catalyst natural lemon juice. All the compounds were evaluated by anti-fungal activity against fungal. The compound having halogens exhibited excellent potent activity. Otherwise, the compounds having electron donating group which exhibited good potent active than that of the electron withdrawing group.

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