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BIOACTIVE, SYNTHESIS SERIES OF 4-(INDOLYL)-6-METHYL-2-THIOXO-1, 2, 3, 4-TETRAHYDROPYRIMIDINE-5-CARBOXYLATE EMPLOYING METHANE SULFONIC ACID

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ABSTRACT

The present study, the synthesis of series a novel 4-(indol-3-yl)- 6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl) ethanone from the reaction of substituted indole -3-carbaldehydes (1.152 mmol), acetyl acetone (1mmol), thiourea(2 mmol) in the presence of two new catalyst methane sulphonic acid at RT conditions. All the compounds were characterized by advanced spectroscopic data (^{1}H NMR, ^{13}C NMR& LCMS) and the structural determination was calculated by elemental analysis. In addition to the all newly synthesized compounds were evaluated by their microbial activity.

KEYWORDS: Acetylacetonate,indole-3-carbaldehydes, methanesulfonicacid, Tetrahydro pyrimidines -2 -thiones, bioevluation.

1. INTRODUCTION

Synthesis of 2-thioxo-1,2,3,4-tetrahydropyrimidines are an important and highly an interesting in organic chemistry as well as medicinally chemistry. This moiety an important key intermediate in organic synthesis. The pyrimidine-2-thione fragment is present in various biologically active molecules and also several therapeutically used.[1-3] Thus, more attention has been paid to analogous of pyrimidine, including their hydrogenation products. This class of moiety contains a broad range of biological and pharmacological activities such as antidepressant[4], calcium antagonist[5,6], antitumor[7], antitubercular[8] anti-inflammatory[9,10], antibacterial and antifungal effects[11,12], analgesic[13,14], antioxidant[15], etc.

Nowadays, the one step processes involving three reactants condensed with using verity of reagents and catalysts are most popular in synthetic organic chemistry for the synthesis of heterocyclic compounds. These single step processes are more convenient as compared with multi step processes as they require shorter reaction times, easy of the product isolation and acquired higher yields and recoveries of the by-product.[16-18]

As part of our in depth study to design and synthesize new pyrimidine-2-thiones derivatives.[19] in the present work ,the synthesis of indole-3-carbaldehyde ,acetyl acetone, thiourea and Bronsted acid catalyst and also use solvent systems at RT condition. The various indole aldehydes having functionalized.

2. METHODS AND MATERIALS

2.1. Experimental

All the chemicals, solvents and synthetic grade reagents were purchased from Fine chemicals and they were used without further purification. The progress of the reaction was monitored by thin layer chromatography (EtOAc: n-hexane = 4:65). The melting point of the all the newly synthesized derivatives were determined open at one end and were uncorrected using an Electrochemical Mk3 apparatus.1HNMR &13CNMR spectrum were recorded on 400MHz Brucker spectrometer in CDCl3 as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me4Si) as an internal standard. Molecular mass of the synthesized compound were determined by LCMS spectrometer. The structures of the compounds can be determined by elemental analysis.

2.2. General procedure for synthesis

A mixture of substituted indole-3-carbaldehyde (1mol), Acetyl acetone (1mol), and thiourea (2mol) are introduced in 50 ml of RB flask. The Brownstd acid

catalyst such as methane sulphonic acid(10ml) was added gradually until the mixture was dissolved .The reaction mixture was carried out on the magnetic stirrer under RT condition. The progress of the reaction was checked by TLC in ethyl acetate: n-hexane (4:6).After completion of the reaction, the mixture was cooled at room temperature and poured on 100 ml crushed ice cold. The crude was filtered and washed with ethyl acetate and a saturated solution sodium bicarbonate in three times. The solid product can be separated by column chromatography (Ethyl acetate: n-hexane, 4:6) as show Scheme - I.

Characterization

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

yellow solid; yield-86%; m.p–243-245^{0}c,^{1}HNMR(400MHz,$CDCl_3$) δ in ppm: 10.124(s,1H,N-H(indole)),9.314(s,1H,N-H(pyrimidine)),9.024(s,1H,N-H(pyrimidine)),7.448(d,J=7.2Hz, 1H, Ar-H),7.126(d,J=8.8Hz,Ar-H),7.087(s,1H,Indole),4.547(s,1H,4(H)),2.145(s,3H,-$COCH_3$), 1.304(s,3H, -CH_3). ^{13}CNMR (100MHz, $CDCl_3$) δ in ppm: 191.87, 187.41, 149.88, and 141.95, LCMS (m/z):384.08.Molecularformula: $C_{21}H_{24}N_2O_5$; Elemental analysis: Calculated: C-65.62, H-6.29, N-7.28. Obtained: 65.54, H-6.28, N-7.36.

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

Paleyellowsolid:yield-93%;m.p–207-208^{0}c;^{1}HNMR(400MHz,$CDCl_3$)δinppm:.10.142(s,1H, N-H(indole)),9.364(s,1H,N-H(pyrimidine)),8.994(s,1H,N-H(pyrimidine)),7.378(d,J=9.0Hz, 1H,Ar-H),7.146(s,1H,Indole),7.078(d,J=8.0Hz,Ar-H),4.584(s,1H,4(H)),1.964(s,3H,-$COCH_3$), 0.929(s,3H,-CH_3);.^{13}CNMR(100MHz,$CDCl_3$)δinppm:191.48,185.65, 147.58,142.45,129.66, 128.84,128.24,127.23,126.67,125.44,123.29,121.47,111.22,54.74,50.77,26.66,18.27.LCMS (m/z):314(M-H). Molecular formula: $C_{16}H_{17}N_3O_2S$. Elemental analysis: calculated: C-60.92, H-5.43, N-13.31. Obtained: C-60.86, H-5.42, and N-13.37.

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

yellowsolid;yield-88%;m.p–227-229^{0}c.^{1}HNMR(400MHz,$CDCl_3$)δinppm:10.447(s,1H,N-H(indole)),9.467(s,1H,N-H(pyrimidine)),9.228(s,1H,N-H(pyrimidine)),7.427-7.287(m,3H, Ar-H), 7.230(s,1H,Ar-H),4.912(s,1H,4(H)),2.516(s,3H,-COCH3),1.628(s,3H,-CH_3). ^{13}CNMR (100MHz,$CDCl_3$)δppm:192.77,189.48,149.56,135.67,129.58,128.63,127.47,127.12,125.79, 124.55,122.87,121.18,109.74,52.19,26.70,19.28.LCMS(m/z):305.45(M+2).Molecular formule: $C_{15}H_{14}FN_3OS$. 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 (4d)

Pale red solid; yield-89%; m.p – 234-236^{0}c :^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 10.629 (s,1H,-NH indole), 9.358(s, 1H, NH Pyrimidine), 9.026(s,1H, NH pyridine), 7.614 (d,J=8.0Hz, 1H,Ar-H), 7.348(d,J=8.6Hz, 1H,Ar-H), 7.266(s, 1H, Ar-H), 7.164(d,J=7.6Hz, 1H,Ar-H), 4.352 (s, 1H, -CH-), 2.268(s, 3H, -$COCH_3$), 2.226-2.110(m, 2H, Ar-H) .^{13}CNMR (100MHz, $CDCl_3$) δ in ppm:194.90, 188.77, 142.56, 133.76, 128.03, 126.22, 124.14, 122.55, 121.63, 119.55, 115.84, 109.47,50.32, 27.42, 17.66. LCMS (m/z): 365.07. Molecular formula: $C_{15}H_{14}BrN_3OS$. Elemental analysis: Calculated: C-49.47, H-3.87, N-11.57, Obtained: C-49.40, H-3.86, N-11.63.

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

Pale pink-solid; yield-90%; m.p – 244-246^{0}c ,^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 10.498(s,1H,N-H(indole)),9.668(s,1H,N-H(pyrimidine)),9.336(s,1H,N-H(pyrimidine)),7.530-7.364(m,3H,Ar-H),7.366 (s,1H,Indole),4.842 (s,1H, 4(H)),2.106(s,3H,-$COCH_3$),1.914(s,3H,-CH_3). ^{13}CNMR (100MHz, $CDCl_3$) δ in ppm: 194.11, 188.56, 151.74, 129.12, 128.58, 125.14, 123.45, 122.44, 121.04, 118.55, 112.75, 108.44, 51.54, and 26.78,17. 66. 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) ethanone (4f)

yellowsolid;yield-86%;m.p–238-240^{0}c:^{1}HNMR(400MHz,$CDCl_3$)δinppm:10.694(s,1H,N-H (indole)),9.712(s,1H,N-Hpyrimidine)),9.478(s,1H,N-H(pyrimidine)),7.512(d,J=8.0Hz,1H, Ar-H),7.244(d,J=8.0Hz,Ar-H),7.198(s,1H,Indole),5.057(s,1H,4(H)),2.544(s,3H,-COCH3), 1.946(s,3H,-CH_3).^{13}CNMR(100MHz,$CDCl_3$)δinppm:195.08,189.45,146.26,137.84,131.36, 128.98,127.44,126.34,125.78,121.22,118.27,110.38,108.40,52.06,26.64,18.45.LCMS(m/z): 330.54.Molecular formula15H14N4O3S. 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

3.1. Anti- Bacterial Activity

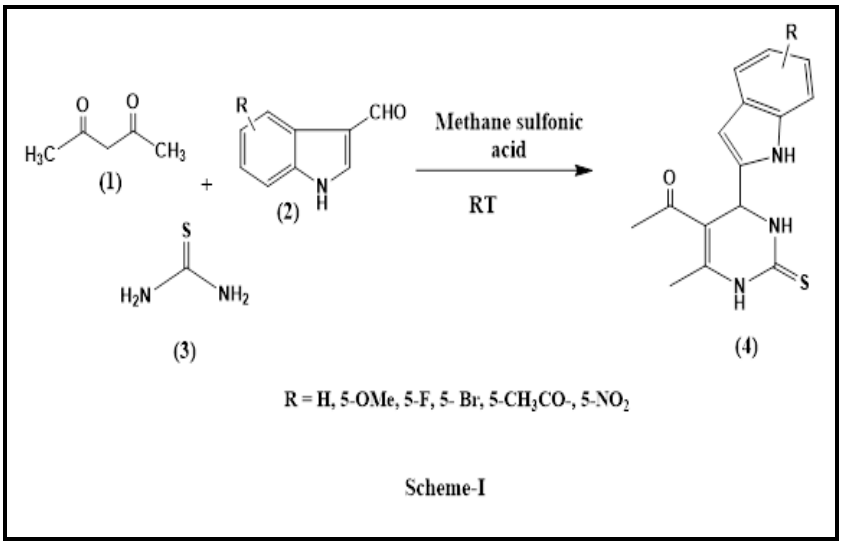
The anti-bacterial activities of newly desired compounds are screened against 4 pathogenic bacteria strains. The results of the bacterial activity were examined for the compounds. The gram negative bacteria were examined Escherichia Coli Pseudomonas aeruginosa. The gram positive bacteria screened were S-aureas and Bacillus .The target compound's a solvent the streptomycin 10 µglml discs were used as a standard. The rest of the compounds were found to be moderate active against the tested micro- organism.

Anti- Fungal Activity

Anti- fungal activities of new synthesized compounds were examined by disc diffusion method against the organism of AspergillusNiger 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 AND DISCUSSION

4.1. Chemistry



Scheme-I

All newly synthesized compounds can be synthesized under at RTC 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 Methanesulphonic acid catalyst. We used various substituted indole -3-carbaldehyde having electron donating group of indole -3- carbaldehyde and electron attracting group of indole -3- carbaldehyde aldehydes and halogen containing indole -3-carbaldehyde aldehydes.

4.2. Biological Activity

All the desired compounds were evaluated by anti-bacterial activity as well as antifungal. Activity. The electron withdrawing group of compounds and electron releasing group compounds exhibited different potent activities. Therefore, electron withdrawing group of compounds exhibited low biological potent activity compared with electron releasing groups. All halogen compounds exhibit well to excellent activity. The compound which possess electron donating group showed moderate activity as shown in Table-I.

Table I: Antimicrobial activity screening activity synthesized scaffold.

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substill	A. Niger	C. albicans
4a	09	08	10	08	07	08
4b	13	12	14	16	09	08
4c	20	19	15	18	14	12
4d	18	20	20	19	15	16
4e	12	11	13	11	10	09
4f	10	14	13	17	09	08
streptomycin	25	25	22	22	NA	NA
Ketoconazole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

5. CONCLUSION

The reaction condition carried at RT condition for all the newly desired derivatives. The yields of the titled compounds were obtained from 86-92%. This compound possesses electron releasing group acquired maximum high yield than that of the compound possesses electron attracting group. The rates of the reaction of the desired compounds are developed by using catalyst methane sulphonic acid. All the compounds are examined by anti-microbial activity against gram positive, gram- negative and fungal. The compound having halogens exhibited excellent potent active .Otherwise the compounds having

electron releasing group which showed better potent active than that of the electron attracting group.

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