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SYNTHESIS, CHARACTERIZATION AND ANTIFUNGAL ACTIVITY OF 3-{4-[6-(SUBSTITUTED PHENYL)-2-THIOXO-1,2,5,6-TETRAHYDRO PYRIMIDIN-4-YL] PHENYL}-6-IODO-2-THIOXO-2,3-DIHYDROQUINAZOLIN-4-ONE DERIVATIVES.

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ABSTRACT

Some new derivatives of 3-{4-[6-(substituted phenyl)-2-thioxo-1,2,5,6-tetrahydro pyrimidin-4-yl] phenyl}-6-iodo-2-thioxo-2,3-dihydroquinazolin-4-one have been synthesized by reacting of 3-{4-[3-(substituted phenyl) prop-2-enoyl]phenyl}-6-iodo-2-thioxo-2,3-dihydroquinazolin-4-one with thiourea and potassium hydroxide (KOH) in 30 ml of ethanol was refluxed for 3 hours. The synthesized compounds were characterized by means of their IR, ^{1}H-NMR spectral data and elemental analysis. All the compounds were tested for their antifungal activities by broth dilution method.

KEYWORDS: quinazolin-4-one, thiourea, ethanol, IR, NMR, Antifungal activity.

INTRODUCTION

In recent years there has been an increasing interest in the chemistry of 4-quinazolinones because of their biological significance. Many of them show antifungal, antibacterial, anticancer, anti -inflammatory, anticonvulsant, immunotropic,hypolipidemic, antitumor, antiulcer and analgesic.[1-13]

From the literature, we found that several quinazolinone derivatives are known to display antimicrobial and therapeutic actives. Literature survey reveals scant mention of the above compounds with antimicrobial properties and hence more and more derivatives are worth tested for the possible medicinal applications. So we have decided to synthesis 3-{4-[6-(substituted phenyl)-2-thioxo-1, 2, 5, 6-tetrahydro pyrimidin-4-yl] phenyl}-6-iodo-2-thioxo-2,3-dihydroquinazolin-4-one.

MATERIALS AND METHODS

All reagents were of analytical reagent grade and were used without further purification, All the product were synthesized and characterized by their spectral analysis, Chemicals Sodium Hydroxide, Hydrochloric acid, potassium hydroxide, thiourea and various aldehyde were purchased from S.D.fine chemicals (india).

Melting points were taken in open capillary tube. IR spectra were recorded on Shimadzu-PerkinElmer F.T I.R. Spectrophotometer Gx and Brooker instrument used for NMR Spectroscopy was 500 MHz and tetramethylsilane used as internal standard. Solvent used were DMSO. Purity of the compounds were checked by TLC on silica- G plates.

EXPERIMENTAL

Step: I Preparation of 3-{4-[3-(substituted phenyl) prop-2-enoyl] phenyl} -6-iodo-2-thioxo-2,3-dihydroquinazolin-4-one (2a-2e).

The solution of 3-(4-acetylphenyl)-6-iodo-2-thioxo-2,3-dihydro quinazolin-4-one in absolute ethanol, substituted benzaldehyde and NaOH were added and refluxed for 10 hours. After refluxing the reaction mixture was concentrated, cooled, filtered and neutralized with dil. HCl. The solid residue thus obtained was crystallized by absolute ethanol.

Step: II Preparation of 3-{4-[6-(substituted phenyl)-2-thioxo-1,2,5,6-tetrahydro pyrimidin-4-yl] phenyl}-6-iodo-2-thioxo-2,3-dihydroquinazolin-4-one (3a-3e)

A mixture of 3-{4-[3-(substitutedphenyl) prop-2-enoyl] phenyl} -6-iodo-2-thioxo-2,3-dihydroquinazolin-4-one, thiourea and potassium hydroxide(KOH) in ethanol was refluxed for 3 hours. After standing overnight the solid formed was collected and crystallized from acetone.

IR (KBr); 3a-3e (cm^{-1}) The characteristic bands of (>NH-) 3500-3470 cm^{-1}, (-OH) 3280 cm^{-1},(-C=S) 1290-1230 cm^{-1}, (-C=N-) 1600-1610 cm^{-1} were obtained for stretching. The stretching vibrations (–C-O-C-) group showed in the finger print region of 1050-1045 cm^{-1} while (-C-Cl-) stretching signal was obtained at 685-680 cm^{-1}. while (-C-I-) stretching signal was obtained at 525-500 cm^{-1} It gives aromatic (-C-H-) stretching frequencies between 2875-2850 cm^{-1} and ring skeleton (-C=C-) stretching at 1585-1570 cm^{-1} , C-H stretching

frequencies for methyl and methylene group were obtained near 1470-1455 cm^{-1}, 1395-1385 cm^{-1} .

1H NMR (DMSO): 3b: 1.88, Doublet (2H) (-CH_2-), 2.51, Doublet (1H) (-NH-), 3.76, Singlet (9H) (-OCH_3), 3.87, Triplet (1H) (-CH<), 4.11, Singlet (1H) (-NH-) 6.41-8.21, multiplate (9H) (Ar-H)

RESULTS AND DISCUSSION

Physical constant of 3-{4-[6-substituted phenyl)-2-thioxo-1,2,5,6-tetrahydro pyrimidin-4-yl] phenyl}-6-iodo- 2-thioxo-2,3-dihydroquinazolin-4-one shown in Table-I.

Antifungal activity

The MICs of synthesized compounds were carried out by broth micro dilution method. Each synthesized drug was diluted obtaining 2000 microgram /ml concentration, as a stock solution.[14-16] The invitro antimicrobial activity of test compounds were assessed against 24 hr cultures of several selected fungi. The fungi used were C. albicans, A. niger, and A.clavatus. The antifungal activity was performed by broth dilution method in DMSO. Nystatin and Greseofulvin were used as standard for the evaluation of antifungal activities respectively. The results are summarized in Table-II.

CONCLUSION

The Main focus of this research work was to synthesize, characterize and evaluate anti fungal activities of the newly synthesized compounds were confirmed and characterized with the help of analytical data's such as IR and 1H-NMR. Biological screening result of activities 3-{4-[6-substituted phenyl)-2-thioxo-1,2,5,6-tetrahydro pyrimidin-4-yl] phenyl}-6-iodo- 2-thioxo-2,3-dihydroquinazolin-4-one derivatives are given below.

ANTIFUNGAL ACTIVITY

Against *Candida albicans* (MTCC 227): The present investigation revealed the maximum antifungal activitywas shown by the compounds 3b, (>1000 µ gm/ml) very good activity against C.albicans *(MTCC 227)* compared with standard drugs of nystatin and greseofulvin, the good antifungal activity was shown by the compounds 3d,3e, (1000 µ gm/ml). While Compound 3a and 3c was shown Equal activity against C.albicans compared with standard drug greseofulvin.

Against *Aspergillus Niger* (MTCC 282): The present investigation revealed the maximum anti fungal activity was shown by the compounds 3a (1200 µ gm/ml), 3d, (>1000 µgm/ml) and the minimum antifungal activity was shown by the compounds 3b,3e, (250 µ gm/ml).

The compounds 3c (500 µ gm/ml) was shown moderate activity against *Aspergillus Niger (MTCC 282)* with the standard drugs nystatin and greseofulvin.

Against *Aspergillus clavatus* (MTCC 1323): The present investigation revealed the maximum anti fungal activity was shown by the compounds 3a (1200 µ gm/ml),3d (>1000 µ gm/ml) and the minimum antifungal activity was shown by the compounds 3c (250 µ gm/ml). The compounds 3b and 3e, (500 µ gm/ml) moderate activity against Aspergillus Clavatus (MTCC 1323) with compared standard drug drugs nystatin and greseofulvin.

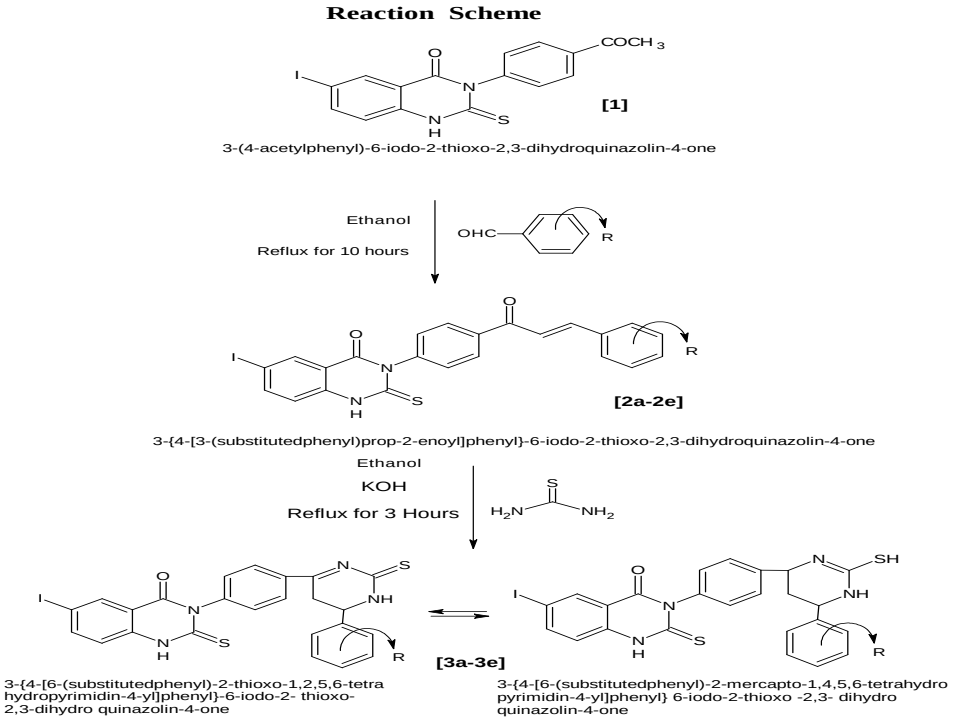
In future 3-{4-[6-substituted phenyl)-2-thioxo-1,2,5,6-tetrahydro pyrimidin-4-yl] phenyl}-6-iodo- 2-thioxo-2,3-dihydroquinazolin-4-one based derivatives will be used for further development of new antifungal agent.

Table: I Physical constant of 3-{4-[6-substituted phenyl)-2-thioxo-1,2,5,6-tetrahydro pyrimidin-4-yl] phenyl}-6-iodo- 2-thioxo-2,3-dihydroquinazolin-4-one.

No.	Sub No.	R	Molecular Formula	Mol.Wt. (gm)	Yield (%)	M.P. \C	Carbon(%)		Hydrogen(%)		Nitrogen(%)	
							Found	required	Found	required	Found	required
1	3a	- 4-Cl	$C_{24}H_{16}ClIN_4OS_2$	602.89	65	264	47.76	47.81	2.61	2.67	9.25	9.29
2	3b	- 3,4,5-$(OCH_3)_3$	$C_{27}H_{23}IN_4O_4S_2$	658.53	75	286	49.18	49.24	3.47	3.52	8.48	8.51
3	3c	- 2- OH	$C_{24}H_{17}IN_4O_2S_2$	584.45	65	255	49.28	49.32	2.86	2.93	9.55	9.59
4	3d	- 4-OH ,-3-OCH_3	$C_{25}H_{19}IN_4O_3S_2$	614.48	68	194	48.80	48.87	3.08	3.12	9.09	9.12
5	3e	- 4-$N(CH_3)_2$	$C_{26}H_{22}IN_5OS_2$	611.52	68	253	51.03	51.07	3.55	3.63	11.41	11.45

Table: II Antifungal activities of 3-{4-[6-substituted phenyl)-2-thioxo-1,2,5,6-tetrahydro pyrimidin-4-yl] phenyl}-6-iodo- 2-thioxo-2,3-dihydroquinazolin-4-one.

SR. NO.	COMP. NO.	R	ANTIFUNGAL ACTIVITY Minimal Inhibition Concentration (μgm/ml)		
			Fungus		
			C.ALBICANS	A.NIGER	A.CLAVATUS
			MTCC 227	MTCC 282	MTCC 1323
1	3a	- 4-Cl	500	1200	1200
2	3b	- 3,4,5-$(OCH_3)_3$	>1000	250	500
3	3c	- 2- OH	500	500	250
4	3d	- 4-OH ,-3-OCH_3	1000	>1000	>1000
5	3e	- 4-$N(CH_3)_2$	1000	250	500
6	Nystatin (standard drugs)	.....	100	100	100
7	Greseofulvin (standard drugs)	.....	500	100	100



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