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Der Chemica Sinica, 2012, 3(4):901-905

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ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis and characterization of 3-{4-[5-substitutedphenyl) isoxazol-3-yl]phenyl}-6-iodo-2-thioxo- 2,3-dihydroquinazolin-4-one

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ABSTRACT

A new series of some 3-{4-[5-(Substitutedphenyl)isoxazol-3-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-dihydro quinazolin-4-one with dioxane, hydroxylamine hydrochloride and potassium hydroxide was refluxed for 10 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 antibacterial and antifungal activities by broth dilution method.

Keywords: Dihydro quinazolin-4-one, dioxane, IR, NMR, Antibacterial and Antifungal.

INTRODUCTION

Compounds incorporating heterocyclic ring systems continue to attract considerable interest due to the wide range of biological activities they posses. Amongst them five membered heterocyclic compounds occupy a unique place in the realm of natural and synthetic organic chemistry. Five membered heterocycles like isoxazoline have found wide application as pharmaceutical and agrochemical agents. In recent years, attention has increasingly been given to the synthesis of isoxazoline derivatives as a source of new antibacterial agents. The synthesis of novel isoxazoline derivatives remain a main focus of medicinal research.

Isoxazoline derivatives have been reported to possess antifungal [1], antibacterial [2], anticonvulsant [3], anti-inflammatory [4], anti-viral [5], analgesic [6], antitumor [7], chemotherapy [8] activity. Penicillin derivatives containing isoxazole ring were found to be antibacterial agent [9]. Isoxazoline derivatives also showed good potency in animal models of thrombosis [10]. In addition, isoxazoline derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis [11-15].

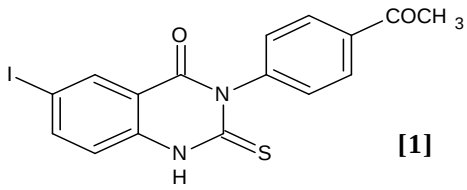
So we have decieded a new series of synthesis 3-{4-[5-(Substitutedphenyl)isoxazol-3-yl]phenyl}-6-iodo-2-thioxo-2,3-dihydroquinazolin-4-one.

MATERIALS AND METHODS

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

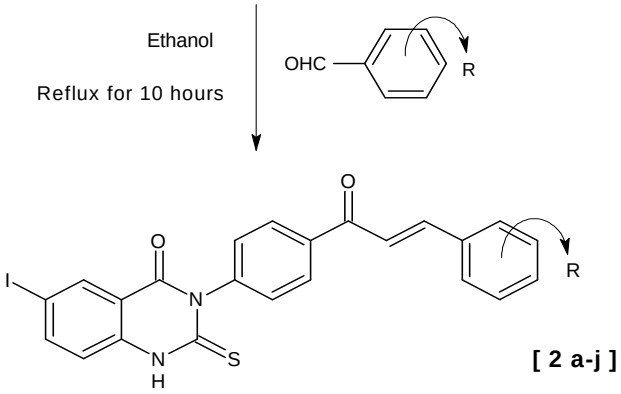
Melting points were taken in open capillary tube. IR spectra were recorded on Shimadzu-PerkinElmer F.T I.R. Spectrophotmeter Gx and Brukker instrument used for NMR Spectroscopy was 500 MHz and tetramethylsilane used as internal standard. Solvent used were DMSO. Purity of the compounds were checked by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

Reaction Scheme



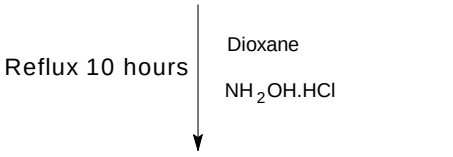
[1]

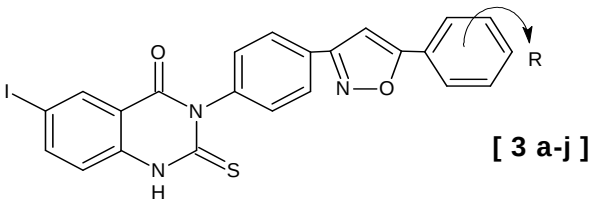
3-(4-acetylphenyl)-6-iodo-2-thioxo-2,3-dihydroquinazolin-4-one



[2 a-j]

3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-6-iodo-2-thioxo-2,3-dihydroquinazolin-4-one





[3 a-j]

3-{4-[5-(substitutedphenyl)isoxazol-3-yl]phenyl}-6-iodo-2-thioxo-2,3-dihydroquinazolin-4-one

Step: I Preparation of 3-{4-[3-(substituted phenyl) prop-2-enoyl] phenyl}-6-iodo-2-thioxo-2,3-dihydroquina zolin-4-one (2 a-j).[16]

The solution of 3-(4-acetylphenyl)-6-iodo-2-thioxo-2,3-dihydro quinazolin-4-one (0.01M) in absolute ethanol (50 ml), substitutedbenzaldehyde (0.01M) and 2% NaOH (10 ml) 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.

IR (KBr); 2g (cm^{-1}) : 3420(>N-H of sec. amine), 3340(-OH), 3060(C-H,

aromatic),1690(>C=O), 1580(>C=C<, aromatic ring),1240(>C=S), 1300(C-N), 1150(-C-O-), 510(C-I).^{1}H NMR (DMSO) : 2j: 3.78, singlate (1H) (-NH-), 7.76, Doublet (2H) (-CH=CH-), 6.64-8.31,multiplate (11H) (Ar-H)

Step: II Preparation of 3-{4-[5-(Substitutedphenyl)isoxazol-3-yl]phenyl}-6-iodo-2- thioxo-2,3-dihydro quinazolin-4-one (3 a-j).[17]

A mixture of 3-{4-[3-(substitutedphenyl) prop-2-enoyl] phenyl}-6-iodo-2-thioxo-2,3-dihydroquinazolin-4-one (0.01M) in 25ml dioxane, hydroxylamine hydrochloride (0.715g, 0.01M) and 40% potassium hydroxide(KOH) was refluxed for 10 hours. Then the reaction mixture was cooled, poured into crushed ice(100g) and neutralized with HCl. The product separated out was filtered, washed with water, dried and recrystallised from alcohol.

IR : 3e (cm^{-1}): 3375(>N-H of sec. amine), 3240(-OH), 3050(=CH), 1700(>C=O), 1600(>C=N), 1520(>C=C<, aromatic ring), 1470(-CH_2), 1320(-C-N),1240(>C=S), 1150(-C-O) 500(C-I).

^{1}H NMR (DMSO) : 3f : 3.65, Singlet (3H) (-OCH_3), 3.76, Singlet (1H) (-NH-), 6.54, Singlet (1H) (-CH=), 6.56-7.99, Multiplate, (10H) (-Ar-H), 9.78, Singlet (1H) (-OH)

RESULTS AND DISCUSSION

Table : I Physical constant of 3-{4-[5-(substitutedphenyl)isoxazol-3-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	Cald.	Found	Cald.	Found	Cald.
1	3a	- 4-Cl	$C_{23}H_{13}ClIN_3O_2S$	557.79	60	178	49.47	49.53	2.32	2.35	7.48	7.53
2	3b	- 2-Cl	$C_{23}H_{13}ClIN_3O_2S$	557.79	58	186	49.47	49.53	2.32	2.35	7.48	7.53
3	3c	- 3,4-OCH_3,	$C_{25}H_{18}IN_3O_4S$	583.39	63	135	51.43	51.47	3.07	3.11	7.15	7.20
4	3d	- 3,4,5-$(OCH_3)_3$	$C_{26}H_{20}IN_3O_5S$	613.42	65	118	50.87	50.91	3.25	3.29	6.80	6.85
5	3e	- 2- OH	$C_{23}H_{14}IN_3O_3S$	539.34	61	148	51.18	51.22	2.57	2.62	7.75	7.79
6	3f	- 4-OH , -3-OCH_3	$C_{24}H_{16}IN_3O_4S$	569.37	63	142	50.61	50.63	2.80	2.83	7.33	7.38
7	3g	- 4-OH	$C_{23}H_{14}IN_3O_3S$	539.34	64	182	51.18	51.22	2.57	2.62	7.75	7.79
8	3h	- 4-$N(CH_3)_2$	$C_{25}H_{19}IN_4O_2S$	566.41	65	162	52.98	53.01	3.35	3.38	9.86	9.89
9	3i	- 4-OCH_3	$C_{24}H_{16}IN_3O_3S$	553.37	67	148	52.03	52.09	2.88	2.91	7.54	7.59
10	3j	- 3- NO_2	$C_{23}H_{13}IN_4O_4S$	568.34	60	157	48.56	48.61	2.27	2.31	9.83	9.86

Table: II Antimicrobial activities of 3-{4-[5-(substitutedphenyl)isoxazol-3-yl]phenyl}-6-iodo-2-thioxo-2,3-dihydroquinazolin-4-one

SR. NO.	COMP. NO.	R	**ANTIBACTERIAL ACTIVITY Minimal Inhibition Concentration(□gm/ml)**				**ANTIFUNGAL ACTIVITY** Minimal Inhibition Concentration (□gm/ml)		
			Gram positive bacteria		**Gram negative bacteria**		**Fungus**		
			s.aureus	***s.pyogenus***	***e.coli***	***p.aeruginosa***	***c.albicans***	***a.niger***	***a.clavatus***
			MTCC 96	MTCC 442	MTCC 443	MTCC 1688	MTCC 227	MTCC 282	MTCC 1323
1	**3a**	- 4-Cl	500	200	125	125	500	1000	500
2	**3b**	- 2-Cl	250	100	200	200	1000	500	500
3	**3c**	- 3,4-OCH3,	200	125	250	250	1000	1000	1000
4	**3d**	- 3,4,5-(OCH3)3	200	200	250	250	500	250	500
5	**3e**	- 2- OH	200	200	62.5	62.5	1000	200	200
6	**3f**	- 4-OH ,-3-OCH3	200	250	125	100	1000	>1000	>1000
7	**3g**	- 4-OH	200	250	200	250	250	>1000	>1000
8	**3h**	- 4-N(CH3)2	200	125	100	100	1000	500	500
9	**3i**	- 4-OCH3	100	200	125	62.5	500	500	500
10	**3j**	- 3- NO2	200	125	200	100	250	1000	500

Table : III Antibacterial activity: Minimal inhibition concentration (The standard Drugs)

Drug	*E.Coli*	*P.Aeruginosa*	*S.Aureus*	*S.Pyogenus*
	MTCC 443	MTCC 1688	MTCC 96	MTCC 442
(Microgramme/ml)				
Gentamycin	0.05	1	0.25	0.5
Ampicillin	100	---	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10s

Table : IV Antifungal activity: Minimal inhibition concentration(The standard Drugs)

Drug	*C.Albicans*	*A.Niger*	*A.Clavatus*
	MTCC 227	MTCC 282	MTCC 1323
(Microgramme/ml)			
Nystatin	100	100	100
Greseofulvin	500	100	100

Physical constant of 3-{4-[5-(substitutedphenyl)isoxazol-3-yl]phenyl}-6-iodo-2-thioxo-2,3- dihydroquinazolin-4-one shown in Table-I.

Antimicrobial 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.[18-21] The invitro antimicrobial activity of test compounds were assessed against 24 hr cultures of several selected bacteria and fungi. The bacteria used were E. coli, S.aureus,P. aeruginosa, and S. pyogenus; the fungi used were C. albicans, A. niger, and A.clavatus. The antimicrobial activity was performed by broth dilution method in DMSO. Gentamycin, Ampicilin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Nystatin and Greseofulvin were used as standard for the evaluation of antibacterial and antifungal activities respectively. The results are summarized in Table-II. The activity was reported by Antibacterial activity of minimal Inhibition Concentration with standard drugs shown in Table:III. The antifungal activity of minimal inhibition concentration with standard drugs shown in Table:IV.

CONCLUSION

The Main focus of this research work was to synthesize, characterize and evaluate antimicrobial 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-[5-(Substitutedphenyl)isoxazol-3-yl] phenyl}-6-iodo-2-thioxo- 2,3-dihydroquinazolin-4-one based derivatives are given below.

ANTIBACTERIAL ACTIVITY:

From screening results, substituted isoxazol compound 3c,3d,(250 µgm/ml) possesses good activity and 3e(62.5 µgm/ml) minimum and poor antibacterial activity against E.coli (MTCC 443),Compound 3a,3d,3g, (250 µgm/ml) better activity and 3e,3i (62.5 µgm/ml) minimum antibacterial activity against P.aeruginosa (MTCC 1688),Compound 3a,(500 µgm/ml) very good activity and minimum and poor antibacterial activity was shown by the compounds 3i, (100 µgm/ml) against S. aureus (MTCC 96),Compound 3f,3g (250 µgm/ml) very good activity and minimum antibacterial activity was shown by the compounds, 3b,(100 µgm/ml) against S. pyogenes(MTCC 442) with the all standard drugs gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin.

ANTIFUNGAL ACTIVITY:

The Present investigation revealed the maximum antifungal activity was shown by the compounds 3b,3c,3e,3f,3h,(1000 µgm/ml) very good activity and the minimum and poor antifungal activity was shown by the compounds, 3g,3i,(250 µgm/ml) against C.albicans (MTCC 227),The compound 3f,3g, (>1000 µgm/ml) better activity and the minimum antifungal activity was shown by the compounds, 3e,(200 µgm/ml) against Aspergillus Niger(MTCC 282),The compound 3f,3g,(>1000 µgm/ml) better actvity and the minimum antifungal activity was shown by the compounds 3e,(200 µgm/ml) The remaing compound good to moderate activity against Aspergillus Clavatus compared with the standard drugs nystatin and greseofulvin.

In future 3-{4-[5-(Substituted phenyl)isoxazol-3-yl] phenyl}-6-iodo-2-thioxo- 2,3-dihydroquinazolin-4-one based derivatives will be used for further development of new antibacterial and antifungal agent.

Acknowledgements
The authors are thankful to the M.N. College, Visnagar for providing research facilities.

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