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"SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-{4-[5-(SUBSTITUTED PHENYL)ISOXAZOL-3-YL]PHENYL}-2-(4-HYDROXYPHENYL)-1,3-THIAZOLIDIN-4-ONE"

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Abstract:
Heterocyclic Compounds have so far been synthesized mainly due to the wide range of biological activities. Isoxazoles plays an important role in biological field. From these reviews we synthesized a new series of 3-{4-[5-(substititedphenyll) isoxazol-3-yl]phenyl}-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one derived from 3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one and hydroxylamine hydrochloride. The title compounds were characterized by element analysis, IR, NMR and spectral data. All the compounds were tested for their antibacterial and antifungal activities by Cup Borer method.
Keywords: *Isoxazoles, IR, NMR, Cup Borer method.*

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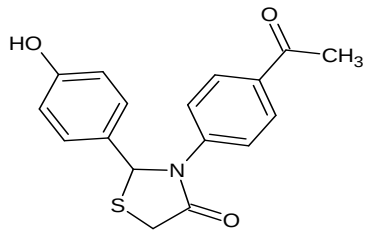
INTRODUCTION:

Heterocyclic compounds have attracted considerable attention as they act as a bridge between chemical and life sciences. A significant amount of contemporary investigation is currently pursued on these compounds worldwide. The chemistry of isoxazoles has been an interesting field of study for decades because of their prominent potential as analgesic[1], anti-inflammatory[2], anticancer[3], antimicrobial[4], antiviral[5], anticonvulsant[6], antidepressant[7] and immunosuppressant[8]. The literature survey revealed that the substitution of various groups on the isoxazole ring imparts different activity. this review summarizes current propensity in the isoxazole synthetic chemistry and divulges the utility of this potent nucleus as a rich source of new compounds having promising biological activities.

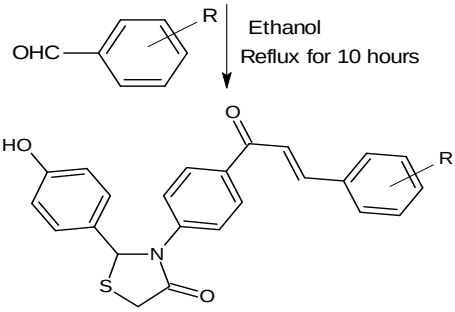
EXPERIMENTAL:

All reagents were of analytical reagent grade and were used without further purification, All the product were synthesized and characterized by their spectral analysis. Melting points were taken in open capillary tube. The IR spectra were recorded on Bruker Model; Alpha, Laser Class1, made in Germany and Brooker instrument used for NMR Spectroscopy was 500 MHz and tetramethyl silane used as internal standard. Solvent used were DMSO. Purity of the compounds was checked by TLC on silica-G plates. Anti-microbial activities were tested by Cup-Borer method.

Reaction Scheme

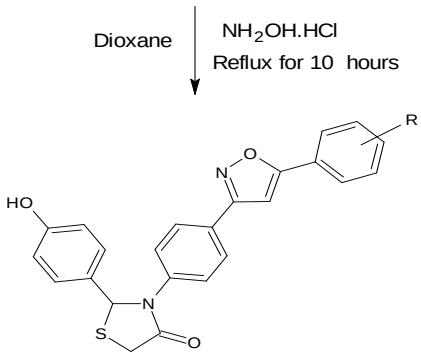


3-(4-acetylphenyl)-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one



1a-1j

3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one



2a-2j

3-{4-[5-(substititedphenyll)isoxazol-3-yl]phenyl}-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one

Preparation of 3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one.(1a-1j)

To the solution of 3-(4-acetylphenyl)-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one (0.01M) in absolute ethanol (50 ml), substituted aldehyde (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(1a)**, cm^{-1}: 3276 (-OH), 3056 (=C-H), 2925 (-C-H stretching), 1725 (>C=O stretching), 1590 (>C=C< Aromatic),1440(-CH_3- bend), 1305 (C-N), 800 (C-Cl), 725 (C-S-C). **^{1}H-NMR (1b-DMSO, δ, ppm)**: 3.358 (2H, s, -CH_2-), 5.843 (1H, s, >CH-), 6.643-7.639 (12H, m, Ar-H), 7.955 (2H, d, -CH=CH-), 9.016 (1H, s,-OH).

Preparation of 3-{4-[5-(substituted phenyl) isoxazol-3-yl] phenyl}-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one (2a-2j):

A mixture of 3-{4-[3-(substitutedphenyl) prop-2-enoyl]phenyl}-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one (0.01M) in 25ml dioxane, hydroxylamine hydrochloride (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 recrystallized from alcohol. **IR(2j), cm^{-1}**: 3223 (-OH), 3098 (=C-H), 2953 (-C-H stretching), 1694 (>C=O stretching), 1605 (>C=N- stretching), 1550 (N=O), 1515 (>C=C< Aromatic), 1460 (-CH_2- bend), 1302 (C-N),1250 (-C-O), 650 (C-S-C) **^{1}H-NMR (2f-DMSO, δ, ppm)**: 3.355 (2H, s, -CH_2-), 3.768 (3H, s, -OCH_3), 5.983 (1H, s, >CH-), 6.600 (1H, s, >-C-CH=), 6.534-7.705 (12H, m, Ar-H), 9.003 (2H, s, -OH)

Table: 1 - ***Physical constant of synthesized compound (2a-2j)***

Comp'd	R	M.F.	Yield %	M.P. °C	Elemental Analysis		
					% C Found (Calcd)	% N Found (Calcd)	% H Found (Calcd)
2a	-2-Cl	$C_{24}H_{17}ClN_2O_3S$	85	179	64.19 (64.21)	6.23 (6.24)	3.80 (3.82)
2b	-4-Cl	$C_{24}H_{17}ClN_2O_3S$	81	170	64.20 (64.21)	6.23 (6.24)	3.81 (3.82)
2c	-3,4- $(OCH_3)_2$	$C_{26}H_{22}N_2O_5S$	87	179	65.80 (65.81)	5.88 (5.90)	4.66 (4.67)
2d	-H	$C_{24}H_{18}N_2O_3S$	67	160	69.52 (69.55)	6.74 (6.76)	4.34 (4.76)
2e	-2-OH	$C_{24}H_{20}N_2O_4S$	73	189	66.64 (66.65)	6.46 (6.48)	4.65 (4.66)
2f	-4-OH-3-OCH_3	$C_{25}H_{20}N_2O_5S$	70	190	65.18 (65.20)	6.06 (6.08)	4.37 (4.38)
2g	-4-OH	$C_{24}H_{18}N_2O_4S$	65	184	66.92 (66.96)	6.49 (6.51)	4.19 (4.21)
2h	-4-$N(CH_3)_2$	$C_{26}H_{23}N_3O_3S$	83	172	68.23 (68.25)	9.13 (9.18)	5.04 (5.07)
2i	-4-OCH_3	$C_{25}H_{20}N_2O_4S$	85	168	67.52 (67.55)	4.52 (4.54)	6.28 (6.30)
2j	-3-NO_2	$C_{24}H_{17}N_3O_5S$	73	176	62.72 (62.74)	9.12 (9.15)	3.72 (3.73)

RESULTS AND DISCUSSION:

Antibacterial activity:

Against Escherichia Coli:

From screening results, substituted derivatives 2g and 2j possesses very good activity against Penicillin and Kanamycin. The compounds 2a and 2d was shown minimum antibacterial activity. Rest of all compounds were found to show good to moderate activity against Saccharomyces as compared to the standard drug Kanamycin.

Against Staphylococcus aureus:

Biological evaluation of present investigation revealed the maximum antibacterial activity was shown by the compound 2c and 2h. The minimum antibacterial activity was shown by the compound 2d. The remaining compounds were found to show good to moderate activity against Staphylococcus aureus as compared to the standard drug Kanamycin.

Antifungal activity:

Against Candida albicans:

Biological evaluation of present investigation revealed the maximum antifungal activity was shown by the compound 2f. The minimum antifungal activity was shown by the compound 2b and 2i. Rest of all compounds were found to show good to moderate activity against Saccharomyces as compared to the standard drug Amphotericin.

Table: 2 : ***Antimicrobial activities of synthesized compound (2a-2j)***

Sr. No.	Comp. No.	R	Zone of Inhibitions in mm		
			Antibacterial activity		Antifungal activity
			E. coli	S. aureus	C. albicans
1	2a	-2-Cl	13	15	17
2	2b	-4-Cl	15	14	16
3	2c	-3,4- $(OCH_3)_2$	18	17	14
4	2d	-H	14	13	13
5	2e	-2-OH	16	15	16
6	2f	-4-OH- 3-OCH_3	15	14	17
7	2g	-4-OH	17	16	15
8	2h	-4-$N(CH_3)_2$	14	17	14
9	2i	-4-OCH_3	16	16	13
10	2j	-3-NO_2	17	14	15
11	SD - 1	Penicillin	15	17	-
12	SD - 2	Kanamycin	17	19	-
13	SD - 3	Baycor 25 w.p.	-	-	18
14	SD - 4	Amphotericin	-	-	20
15	Solvent	DMF	11	12	12

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