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Synthesis and Antimicrobial Assay of Some Ketoanils and their Thiazolidinones

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ABSTRACT

Nine kitoanils obtained by condensation of primary amines with thiophene glyoxal were used as precursors for the synthesis of thiazolidinones by their cyclocondensation with thioglycolic acid. The chemical structures of the synthesized compounds were confirmed by elemental analysis, molecular weight determination, IR and ^{1}H NMR spectral measurements. Antibacterial and antifungal properties were studied in vitro against four bacteria and two fungi by using ampicillin and grislofulvin reference drugs respectively.

Key words: Kitoanils, Thiophene glyoxal, Antibacterial and antifungal.

INTRODUCTION

Schiff's bases, obtained by condensation of carbonyl compounds and primary amines, containing diverse substituent's, owing to >C = N – linkage are widely used as precursors in the synthesis of variety of organic molecules[1-3] and exhibit wide spectrum of interesting biological properties, viz. anticancer[4], antiviral[5], pesticidal[6], antibacterial[7-9], antifungal[10-11] etc. There has been a steady growth of interest in the synthesis, structure and reactivity of Schiff bases due to their potential applications in biological modeling, design of molecular magnets and materials chemistry[12-13]. Schiff bases have also been extensively used as ligands in coordination chemistry owing to their nice donor abilities[14-15]. Metal complexes of Schiff bases have diverse industrial applications, especially in catalysis[16-17] dyeing[18-19] and analytical reagents[20-21].

Among the small ring heterocyclic's containing nitrogen and sulphur 4-thiazolidinones have been under investigation for a long time because of their excellent biological properties such as antibacterial[22-23], antifungal[22-23], antituberculostatic[24-25], anti-HIV[26], anticancer[27], anticonvulsant[28], anti-inflammatory[29], analgesic[29] etc. The biological significance of this class of compounds and multidrug resistance of several Gram-positive microbes impelled us to continue working on the synthesis and antimicrobial screening against some typical Gram-positive bacteria and fungi of new thiazolidinone derivatives. In the present study we report synthesis, characterization and antimicrobial evaluation against some important microbes of new 2-(2-ketothiophene-yl)-3-(substituted aryl)-1-thiazolidin-4ones.

EXPERIMENTAL

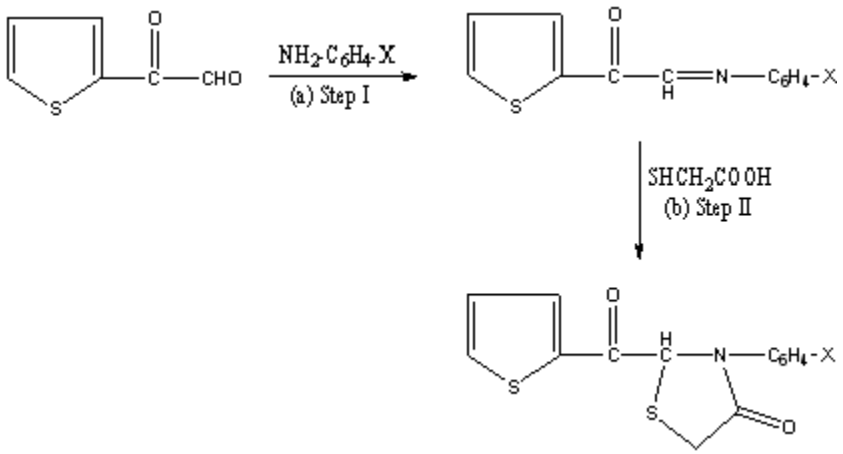
Synthesis scheme

Synthesis of 4-thiazolidinones involved two steps

Reagents and conditions

(a) Primary amines, 2- thiophene glyoxal, acetic acid-ethanol (1:15, v/v), reflux ~ 2h.

(b) Ketoanil, thioglycolic acid, dry benzene, reflux ~ 9h.



Where, X=H; o-, m-, p-NO_2; o-, m-, p-CH_3; p-Cl; p-OCH_3

Scheme 1:

Step I

All the ketoanils[28] were synthesized by condensing the equimolar (1: 1) mixture of each primary amine with 2-thiophene glyoxal[30] in acetic acid-ethanol (1:15, v/v) followed by refluxing for 2-5 h. Reaction mixtures were concentrated on water bath and products were precipitated with ether. Finally all the products were washed with ether repeatedly and dried in air. The synthesized compounds were crystallized from n-hexane.

Step II

For the synthesis of 4-thiazolidinones reactants, ketoanil (0.05 mol) and thioglycolic acid (0.010 mol, 98%), were mixed together in dry benzene and refluxed for 8-10 h. To the concentrated reaction mixtures aqueous solution of sodium bicarbonate was added with continuous stirring to neutralize the unreacted acid. Precipitates obtained were filtered out, washed with water and dried in air. The products were crystallized from ethanol/ methanol.

The purity of the synthesized compounds was checked by thin-layer chromatography. Almost all the samples showed single spot migration on silica gel thin-layers. Impure samples were purified either by column chromatography or by washing with solvent as identified by TLC.

Physico-chemical and Antimicrobial studies

Microanalysis for carbon, hydrogen, nitrogen and sulphur contents of the products were done on Vario-el-III, elemental-R analyzer. Melting points determined in open glass capillaries were uncorrected. Infrared spectra were recorded in KBr medium on Thermo Nicolet Nexus FT-IR spectrometer. ^{1}H NMR spectra were recorded in dimethyl sulphoxide solvent on Bruker-400 Mhz spectrometer. Molecular weights of the compounds were determined by Rast›s method[31] with camphor as solvent.

The minimum inhibitory concentration (MIC) of the samples was determined by the micro broth dilution technique using Mullar Hinton broth against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aerugionsa, Candida albicans* and *Aspergillus niger* microorganisms. Serial two- fold dilutions ranging from 400 µg/ml to 25 µg/ml in DMSO - water (1:4,v/ v) were used. Muller Hinton broth was used as

Table 1 : Colour, yield, melting point, molecular weight and analyses data of compounds

Compd	Colour	Yield	M.P.	M.W.calcd.	Analyses (%) : Calcd.(Found)			
		(%)	(^{0}C)	(Found)	C	H	N	S
1a	Light brown	81	194	260 -	55.17 (55.90)	3.06 (3.16)	10.72 (10.31)	12.26 (12.80)
1b	Brown	85	125	260 (264.6)	55.17 (54.92)	3.06 (3.42)	10.72 (11.07)	12.26 (12.03)
1c	Yellow	88	166	260 (256.1)	55.17 (55.26)	3.06 (3.12)	10.72 (11.06)	12.26 (12.17)
1d	Cream	84	202	229 -	68.12 (68.72)	4.80 (5.21)	6.11 (6.48)	13.97 (14.56)
1e	Skin	87	199	229 -	68.12 (68.38)	4.80 (5.38)	6.11 (5.76)	13.97 (13.49)
1f	Light brown	92	217	229 -	68.12 (67.94)	4.80 (4.61)	6.11 (5.90)	13.97 (13.61)
1g	Silver	89	212	245 -	63.67 (63.08)	4.48 (4.92)	5.71 (6.11)	13.06 (13.51)
1h	Brown	87	99	249.5 (248.1)	57.71 (57.27)	3.20 (3.47)	5.61 (5.33)	12.82 (12.32)
1i	Mudy	88	119	215 (214.6)	66.97 (67.42)	4.18 (4.53)	6.51 (6.89)	14.88 (15.09)
2a	Skin	43	154	334 (330.8)	50.29 (50.74)	2.99 (2.75)	8.38 (8.45)	19.16 (19.19)
2b	Brown	45	74	334 (317.6)	50.29 (51.01)	2.99 (3.08)	8.38 (8.63)	19.16 (19.12)
2c	Light yellow	55	121	334 (330.8)	50.29 (49.91)	2.99 (2.83)	8.38 (8.90)	19.16 (19.61)
2d	Skin	53	194	303 -	59.40 (59.91)	4.29 (4.04)	4.62 (5.04)	21.12 (20.63)
2e	Coffee	62	206	303 -	59.40 (59.22)	4.29 (4.04)	4.62 (4.47)	21.12 (21.81)
2f	Light brown	67	222	303 -	59.40 (59.60)	4.29 (4.69)	4.62 (4.46)	21.12 (20.65)
2g	Silver	77	218	319 -	56.42 (57.80)	4.07 (3.87)	4.38 (4.24)	20.06 (19.76)
2h	Brown	83	99	323.5 (330.8)	51.93 (51.89)	3.09 (3.34)	4.32 (3.98)	19.78 (19.73)
2i	Skin	75	159	289 (283.6)	58.13 (57.66)	3.80 (4.14)	4.84 (4.83)	22.14 (22.39)

Where;

1- C_5H_3SO-CH=N-ArX, 2- C_5H_3SO- C_3H_3NSO-ArX

a: O-NO_2 b: m-NO_2 c: p-NO_2 d: o- CH_3 e: m-CH_3 f: p-CH_3 g: p-OCH_3 h: p-Cl i: H

nutrient medium to grow and dilute the drug suspension for test. The inoculam was prepared using 4-6 h broth culture of each microbe adjusted to a turbidity equivalent to a 0.5 to 0.6 optical density, diluted to broth media to give a final concentration in Elissa plate. The plates were covered with sterilized aluminium foil to prevent evaporation. The plates were incubated at~37^{0}C for 24 h for bacteria and 48 h fungi. DMSO diluent was used as negative control whereas media with ampicillin (standard antibiotic) and grislofulvin (standard antifungal drug) were used as the positive controls.

RESULTS AND DISCUSSION

Theoretically proposed molecular formulae of the compounds are in conformity of experimental data of molecular weights and analyses (Table-1).

All the ketoanils were synthesized by the different method to the reported one [28] and structures were again confirmed by their elemental, IR and ^{1}H NMR analyses. Azomethine and its adjacent ketonic group of the products displayed their stretching vibrations in 1561-1623 cm^{-1} and 1616-1730 cm^{-1} region respectively, whereas one or two bands of thiophene ring υC-S-C occurred in 635-731 cm^{-1}. ^{1}H NMR spectra displayed multiplet peaks of 4H's of benzene ring in δ 6.02-7.95 range and singlet band for ^{1}H of azomethine group in δ 7.60-9.92 region. However methyl and methoxy groups 3H chemical shifts were displayed at δ 2.15-2.52 and δ 3.79 respectively.

The perusal of infrared spectra of 2-(2-ketothiophenyl)-3-(substituted aryl)-1-thiazolidin-4-ones, the cyclocondensation products of ketoanils and thioglycolic acid, revealed one or two bands corresponding to υC = O (cyclic), υC -N and υC -S-C vibrations of thiazolidinone ring at ca. 1696 cm^{-1}, ca. 1320 cm^{-1} & ca. 1355 cm^{-1} and ca. 674 cm^{-1} & ca. 640 cm^{-1} respectively. The presence of these bands and absence of azomethine peak in the products evicts success of cyclocondensation reactions. υC =O (chain), υC =C & υC- H(aromatic), and δ C-H, υC-H symmetric & υC-H asymmetric (CH_2) vibrations in the spectra of the synthesized compounds have been occurring at ca. 1637 cm^{-1} , ca. 1554 cm^{-1}, ca. 1503 cm^{-1} ca. 1472 cm^{-1} & ca. 3072 cm^{-1}, and ca. 1478 cm^{-1} , ca. 2858 cm^{-1} & ca.

Table 2: The minimum inhibitory concentration (MIC, µg/ml) of compounds

Compound	Microorganisms					
	B.subtilisa	***S.aureusa***	***E.coli*^{B}**	***P.aeruginas***	***C.albicans***	***A .niger***
1a	50	-	50	25	25	25
1c	50	100	50	25	50	25
1d	25	25	25	50	25	25
1e	25	25	50	50	25	25
1f	25	25	25	200	25	25
1g	25	25	50	50	25	25
1h	50	50	50	50	25	25
1i	25	25	25	25	25	25
2a	50	25	50	25	25	25
2b	50	50	50	50	-	-
2c	100	50	100	50	25	25
2e	50	50	100	50	25	25
2g	50	50	50	50	50	25
2h	50	-	50	50	-	-
2i	25	50	25	50	25	25
Ampicillin	64	100	64	100	-	-
Grislofulvin	-	-	-	-	80	80

2925 cm^{-1} respectively. The 1H NMR spectra of the products displaying chemical shifts in δ 5.99-8.28, δ 5.25-6.06, δ 1.99- 2.32 and δ 3.79 regions corresponding to 4H of benzene ring, 2H of heterocyclic CH_2 group, 3H of CH^3 and OCH_3 groups respectively are consistent with the structural inferences derived by infrared spectral studies.

The MIC values (Table-2) reveal better bactericidal and fungicidal properties of ketoanils(1a-i) than thiazolidinones (2a-i) in general against test microbes, and interestingly better than reference drugs. The compounds 1d, 1e, 1f, 1g, 1i and 2i, which exhibited highest MIC values as compared with others and reference drugs against test bacteria and fungi, could be proposed for further investigations in view of their usage as drugs.

The effect of the nature of substituted group on the activity of the test microbes has been studied on para- substituted ketoanils and their thiazolidinone products as at this position steric effect is minimum as compared with other positions. In ketoanils the order of bactericidal and fungicidal activities, $OCH_3 \geq Cl \geq NO_2$, is in accordance with electron withdrawing nature of the substituents against all the test microbes except *P. aeruginosa* whereas almost in all the thiazolidinones reverse sequence is obtained.

The effect of the position of substituted group was studied on nitro and methoxy compounds of both series. Invariably all the compounds exhibits ortho ≥ meta ≥ para sequence in antimicrobial properties whereas order in antifungal activities is o > p > m.

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