Synthesis, Characterizationand Anti-Bacterial and Anti-Fungal Activity of Thiazolidin – 4 – One Derivatives

C. Geetha Priya

Department of Pharmaceutical Chemistry,
R. R. College of Pharmacy, Bangalore, India

Manoj Singh

Department of Pharmaceutical Chemistry,
R. R. College of Pharmacy, Bangalore, India

Shilpashree A. T.

Department of Pharmaceutical Chemistry,
R. R. College of Pharmacy, Bangalore, India

ABSTRACT

The Titled compounds have been synthesized by using the reaction among benzoyl chloride and anthranilic acid in presence of pyridine to form intermediate benzoxyzene-four-one which turned into similarly treated with hydrazine hydrate followed by means of condensation of the resulting hydrazones at different aldehyde gives the corresponding schiff's base compounds (5a-e). Reaction of the schiff's base compounds with thioglycollic acids furnishes the goal thiazolidin-4-one molecules (6a-e). The newly synthesized compounds had been screened for anti-bacterial and anti-fungal interest via disc diffusion method. Ciprofloxacin and ketaconazole had been used as a preferred for anti-bacterial pastime and anti-fungal pastime respectively.

Keywords: Schiff's bases, Aromatic aldehyde, Anti-bacterial activity, Anti-fungal activity, Thioglycollic acid.

INTRODUCTION:

Thiazolidinones are the derivatives of thiazolidine which belongs to an important group of heterocyclic compounds[1].Aliterature survey reveals that extensive work has been carried out on the synthesis of thiazolidin-4-one derivatives and known to exhibits various biological activities asanti-microbial, anti-tuberculosis, anti-inflammatory, bronchodilator, antihistaminic, anti-hypertensive, anti-gastric, anti-fertility[7],anti-pyretic[7],analgesic[7], anti-ulcer and anti-bacterial activities. Schiff's base gives good anti-bacterial activity and had several pharmacological applications. This schiff's bases can be prepared by the reaction of aldehyde or ketone which shows good fungicidal activity[10]. In this work we have synthesized somethiazolidin-4-one derivatives to evaluate itsanti-microbial activity against some selected microbes. The structures of the various synthesized compounds were elucidated on the basis of IR, HNMR spectral data and elemental analysis.

MATERIALS AND METHODS:

The melting points were determined in an open capillary tube and are uncorrected. The purity of the newly synthesized compounds were checked by TLC on silicagel GF 254 and spots visualized by iodine vapour, elemental analysis was carried out in vario el 11/ carloebra 1108. IR spectra were recorded in KBR discs on a shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded on GSX 400 with300 MHz; $CDCl_3$ was used as a solvent. Chemica lshift are reported asδ(ppm).

DRUGSANDCHEMICALS:

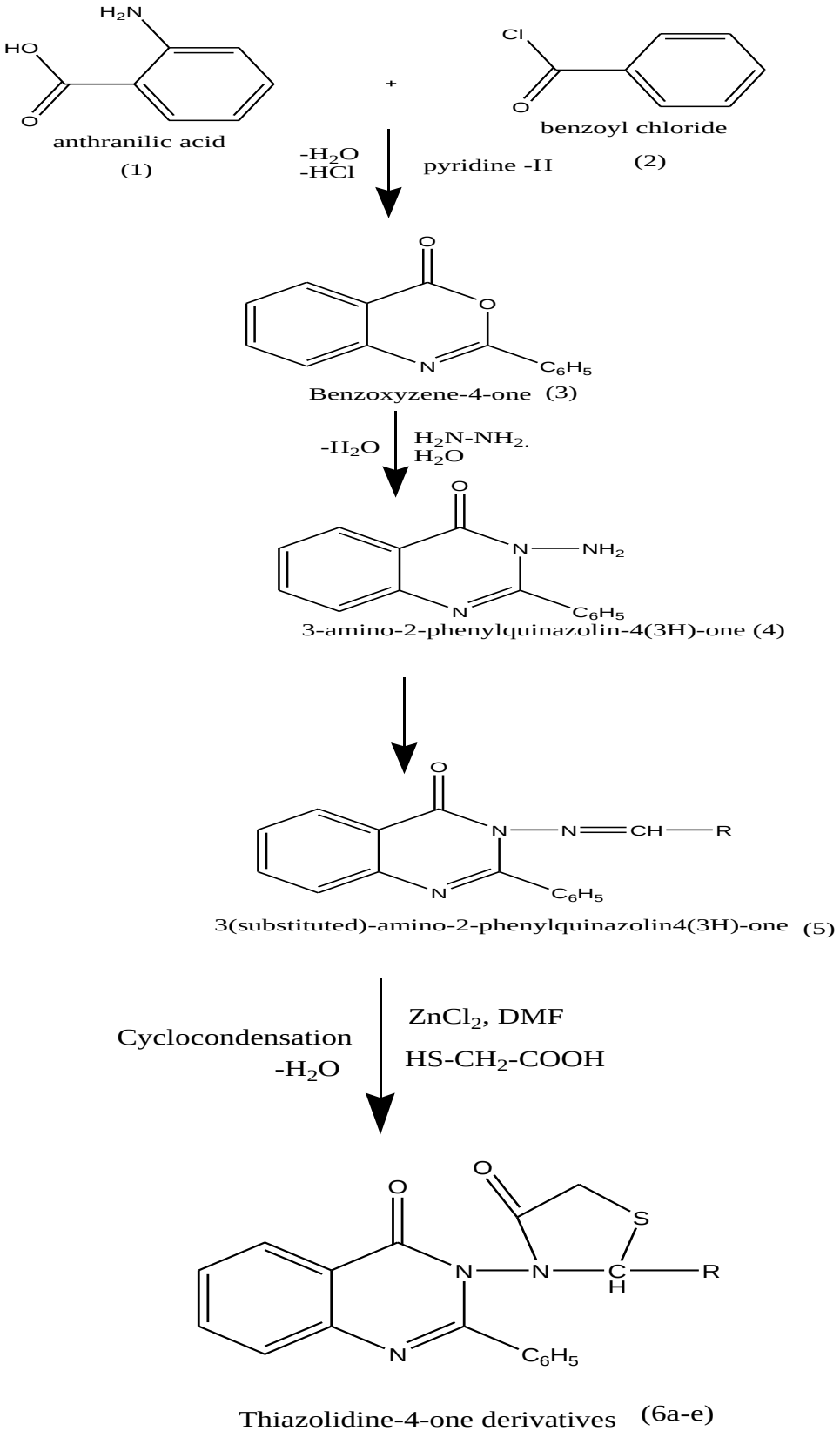
Benzoylchloride, pyridine, anthranilic acid, benzaldehyde, 2-chlorobenzaldehyde,2-nitrobenzaldehyde, anisaldehyde, salicylaldehyde, dry piperidine, dimethyl formamide and ethanol were obtained from Loba chemicals Pvt. Ltd, India and hydrazine hydrate and thioglycollic acid were obtained from Hi Media LaboratoriesLtd.,Mumbai,India.

Synthesis of benzoxyzene-4-one compound:
Scheme – 1
The solution of benzoyl chloride (0.03mole) (4.2 ml) (1) and anthranilic acid (0.02mole) (2.74) (2) gms in dry pyridine (30 ml) is refluxed on water bath for 3Hrs at 35°C. The reaction mixture was cooled and poured into cold dilute hydrochloric acid. The solid benzoxyzene-4-one (3) thus obtained is filtered and recryatallized from benzene.

Synthesis of 3-amino-2-phenylquinazolin-4(3H)-one:
Scheme–2
An intermediate mixture of benzoxyzene4-one (3) compound (0.036mole) (8 gms) and hydrazine hydrate (6 ml) is refluxed in water bath using ethanol (30 ml) as solvent for 6 Hrs at 45°C, then the reaction mixture3-amino-2-phenylquinazolin-4(3H)-one (4) is poured into cold water, filtered , dried and recrystallized from ethanol.

Synthesis of some intermediates 5 (a-e):
Scheme – 3
An equimolar mixture of the 3-amino-2- phenylquinazolin-4(3H)-one (0.01mole) (4) and the appropriate aromatic aldehyde (0.015mole) in absolute n-butanol (50 ml) is heated under reflux on water bath for 2 Hrs in 45°C in the presence of 2 drops of dry piperidine to get various aldehyde derivatives of 3(substituted)- amino-2-phenylquinazolin-4(3H)-one 5(a-e)

Synthesis of thiazolidin-4-one derivatives 6(a-e)
Scheme – 4
A mixture of Schiff's base of 3(substituted)-amino-2-phenylquinazolin4(3H)-one (6 a-e) (0.005moles) which was obtained from Scheme 3 was refluxed with thioglycollic acid and dimethyl formamide (15 ml) containing a pinch of anhydrous zinc chloride for 6 Hrs at 450˚ C. The reaction mixture was then cooled and poured in to crushed ice. The solid (6a-e) thus obtained was filtered and recrystallized from ethanol. The structures of the various synthesized compounds were assigned on the basis of elemental analysis, IR, and ^{1}HNMR spectral data. Spectral and analytical data of the title compounds (6a-e) are shown in Tables 1 . The compounds are evaluated for their anti-inflammatory activity, and results are summaries in Table 2. From the, anti-inflammatory activity it was observed that all the compounds exhibited activity against all the organisms employed. Where as compound (6a-e) showed moderate to good activity.



CHARECTERISATION OF THIAZOLIDINE -4-ONE DERIVATIVES:

3-(4-oxo-3-(4-oxo-2-phenylquinazolin-3(4H)yl)thiazolidin-2-yl)benzaldehyde(6a)

Light yellow solid recrystallized from ethanol, yield - 82%, m.p- 166-168°C, IRKBr-1645,1915,2559and 3072cm^{-1};^{1}HNMR (300 MHz $CDCl_3$) δ 3.38 (s, 2H),5.92(s, 1H),7.9(m,1H), 7.4(m,1H), 7.5(m, 1H), 7.62 (m, 1H), 7.29 (m, 1H), 7.14(m,1H).

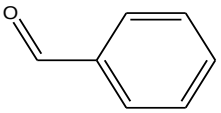
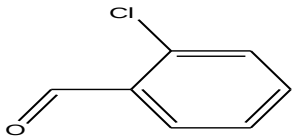
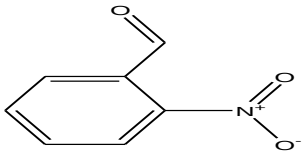
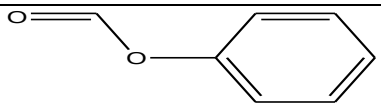
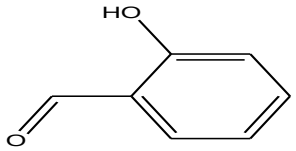
2-chloro-3-((4-oxo-2-phenylquinazolin-3(4H)yl)thiazolidin-2-yl)benzaldehyde(6b)
Pale yellow solid recrystallized from ethanol, yield - 82%, m.p-166-168°C, IRKBr-1588,1684,2855and 3068cm^{-1};^{1}HNMR (300 MHz $CDCl_3$) δ 3.38 (S, 2H),5.92(s, 1H),7.4(m,1H), 7.5(m,1H), 7.6(m,1H),7.29(m,1H),7.9(m,1H).

2-nitro-3-((4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-2-yl)benzaldehyde(6c)
Pale yellow solid, recrystallized from ethanol, yield - 82%, m.p- 166-168°C, IRKBr-1607,1869,2487,2963and3028 cm^{-1};^{1}HNMR (300MHzCDCl$_3$) δ2.35(s,3H), 3.9(s,2H), 5.29(s,3H), 6.94 (s,1H),6.95 (m,1H),7.15 (m,1H),7.29 (m,1H).

4(4- oxo3(4 -oxo- 2- phenyl quinazoline 3 (4H)- yl- thiazolidine 2yl Benzaldehyde(6d)
Pale yellow solid ethanol, recrystallized from ethanol, yield - 82%, yield - 82%, m.p- 166-168°C, IRKBr-1654,1949,2603and3010cm^{-1};^{1}HNMR (300 MHz $CDCl_3$) δ 3.38 (m, 2H),5.92(s,1H),6.95(m,1H),7.29(m,1H),7.4(m,1H),7.5(m,1H),7.62(m,1H),9.6(s,1H).

3-hydroxy-4-(4-oxo-3- (4-oxo-2-phenyl Quinazolin-3 (4H)-yl) thiazolidin-2-yl) benzaldehyde (6e)
Pale yellow solid ethanol, recrystallized from ethanol, yield - 82%, yield - 82%, m.p- 166-168°C, IRKBr - 1639, 2591, 2726 and 3043cm^{-1}; ^{1}HNMR (300 MHz $CDCl_3$) δ 3.38 (m, 2H),5.9 (s, 1H), 7.2 (m, 1H), 7.62 (m, 1H), 7.9(m,1H),9.8(s,1H).

Table 1

Compound Code	R	Molecular Formula	Mol. Wt	R_f	Found % (Calc %)		
					C	H	N
6a	 benzaldehyde	$C_{24}H_{17}N_3O_3S$	399.46	0.6	69.15 (72.09)	4.29 (4.26)	12.55 (10.52)
6b	 2-chloro benzaldehyde	$C_{24}H_{17}ClN_3O_3S$	433.07	0.8	63.66 (66.51)	3.72 (3.92)	9.68 (9.69)
6c	 2-nitro benzaldehyde	$C_{24}H_{16}N_4O_3S$	472.47	0.7	61.87 (61.01)	4.06 (3.38)	12.55 (11.86)
6d	 anisaldehyde	$C_{24}H_{17}N_3O_4S$	443.47	0.8	65.00 (65.01)	3.86 (3.83)	9.48 (9.48)
6e	 salicylaldehyde	$C_{24}H_{18}N_3O_4S$	444.47	0.9	65.12 (64.86)	3.86 (4.05)	9.48 (9.45)

ANTI-BACTERIALACTIVITY:

The newly synthesized compounds were screened for their anti-bacterial activity by the disc diffusion method against two gram negative bacteria *(Pseudomonasarginosa* ATCC-29212, *E.coli ATCC 750*and two gram positive bacteria *(BacilluscerusATCC10987*and*Staphyloccusaureus ATCC-25923*). The agar medium

was purchased from HI media Laboratories Ltd.,Mumbai, India. Preparation of nutrient agar, sodium chloride, meat of beef extract ,and peptone water was done as per the standard procedure. Disc measuring 5 mm in diameter (made from whatmann filterpaper [No.2] sterilized in isopropyl alcohol were dipped in solutions containing synthesized compound, standard and blank were placed on surface of agar plates. The plates were left standing for one hour at room temperature as a period of pre incubation diffusion to minimize the effect of variation in time between the applications of different solutions. Then the plates were incubated at 37°C for 24 hours and observed for antibacterial activity.The diameters of zone of inhibition were measured for plates in which the zone of inhibition was observed and presented inTable1.The test compounds were prepared in different concentrations using dimethyl sulphoxide as a solvent at a concentration of 100mg/ml. Standard (Ciprofloxacin 50 mg/ml) was used for the comparison of anti-bacterial activity. All the experiments were carried out in triplicate.

ANTI-FUNGALACTIVITY:

All those compounds screened for anti-bacterial activity also tested for their anti-fungal activity using sabouraud dextrose agar media by same disc diffusion method against *aspergillus niger ATCC 6275* and *candida albicans ATCC10231).* The agar medium was purchased from HI media Laboratories Ltd., Mumbai,India. Preparation of media was done as per the standard procedure. The solutions of test compounds were prepared by a similar procedure described under the antibacterial activity. Each test compounds were prepared in different concentrations of 100 mg/ml. Standard ketaconazole 50mg/ml was used for the comparison of anti-fungal activity. All the experiments were carried out in triplicate.

DISCUSSION:

The newly synthesized compounds (6a-e)were screened for their anti-bacterial against two grampositivebacteriaviz.,*Bacilluscerus*(*ATCC10987),Staphyloccusaureus (ATCC-25923)*andtwo gram negative bacteria *Pseudomonasarginosa (*ATCC-29212), *E.coli (ATCC750* andanti-fungal activity against *as per gillusniger (ATCC6275)* and *candida albicans (ATCC10231)* by usingdisc diffusion method. Ciprofloxacin and Ketaconazole were used as a standard for anti-bacterial and anti-fungal activity respectively. Compounds (a and e) showed good, compounds (b and c) showed moderate and compound(d) showed weak anti-bacterial activity against *Pseudomonasarginosa*. Compounds (b and e) showed good, compound (a) showed moderate and compounds (c and d) showed weak anti-bacterial activity against *E.coli.* Compound (e) showed good, compounds(a,b,c and d)showed moderate anti-bacterial activity against *Bacilluscerus.* Compounds(a,d and e) showed good, compounds (b and c)showed moderate anti-bacterial activity against *Staphyloccus aureus* when compared with standard ciprofloxacin. Compound(e) showed good, compounds (b, c and d) showed moderate and compound(a) showed weak anti-fungal activity against *candida albicans,* Compound(e) showed good, compounds (a and b) showed Moderate and compounds (can d d) showed weak anti-fungal activity against *aspergillus niger*.

CONCLUSION:

The present study showed that the synthesis of various aldehyde derivatives of thiazolidin-4-one.The synthesized compounds were characterized by spectral studies and the reaction completion was confirmed by TLC using methanol and petroleum ether (3:1) as a solvent system(The solvent system was selected by trial and error method).The synthesized compounds were evaluated for anti-microbial activity. From the antimicrobial evaluation of synthesized compounds, it is very clear that the tested compounds showed near to equipotent activity to that of standard ciprofloxacin and ketaconazole for the study. From anti-microbial activity of evaluations it was found that synthesized compounds showed significant activity against various micro organisms. Perhaps the compounds which contains hydroxyl group have been exhibited more anti-microbial activity than the other compounds. These results suggest that these derivatives have excellent scope for further development as commercial anti-microbial agents. Further experiments needs to elucidate the mechanism of action.

Table:1Anti-bacterialactivityofsynthesizedcompounds.

S.No	Compounds	ZoneofInhibition			
		P.Aeruginosa	***E.Coli***	***B.Cereus***	***S.Aureus***
1	Control	0	0	0	0
2	Standard	24.32±0.21	27.15±0.31	26.20±0.14	27.98±0.12
3	6a	21.33±0.28	18.83±0.86	21.50±0.50	25.96±0.15
4	6b	19.50±0.50	21.33±0.57	20.46±0.56	19.30±0.20
5	6c	17.33±0.57	16.82±0.76	18.70±0.60	20.80±0.10
6	6d	15.50±0.50	17.16±0.28	18.46±0.50	26.23±0.25
7	6e	23.16±0.76	25.16±0.76	24.90±0.46	27.13±0.15

Table:2 Anti-fungalactivitiesofsynthesizedcompounds

S.No	Compounds	ZoneofInhibition	
		C.Albicans	***A.Niger***
1	Control	0	0
2	Standard	26.12±0.23	27.96±0.21
3	6a	15.96±0.95	20.23±0.20
4	6b	20.33±0.30	22.10±0.36
5	6c	18.90±0.55	18.00±0.10
6	6d	21.30±0.55	18.86±0.80
7	6e	25.30±0.30	27.20±0.20

REFERENCES:

Agarwal OP. Text book of Organic Chemistry, pp730.

Bama K, Garnalk, Rajani K Behera. (1988). Synthesized the anti-microbial activity of some 2-arylimino – 4 – tetra - o- acetyl beta–D-gluco pyranosy l-4-thiozolidinones. *Indian J Chem B,* 27(B):1157-1158.

Dhar KL, Sharma SC ,Uzutshi. (1999). The structure and elucidation of two more metabolities of 7, 8, 9, 10 – tetra hydroazepino - [2,1-b] quinazoline – 12 (969H) -one, a potent bronchodilator. *Indian J Chem B*, 38(B):814-817.

JoshiHS, Thaker KM, Kaclhadia VV. (2003). Synthesized of 4 – thiozolidinone and 2-azetidin ones bearing benzothiophene nucleus as potential anti-tubercular and anti-microbial agents. *Indian J Chem B*, 42(B):1544–1547.

Lakshmi Narayanan B, Kumar EP, Pradeep RajKumar LA.Pharmacognistical, Phytochemical investigation and anti-microbial studies on various fractions of Evolvulus alsinoids linn. *Int J AdvPharm Biol Sci* 2012;

2(2): 141-149

Mhogale, Uthale A. Synthesized biological activity of 4-(N-arylidene acetyl hydrazido) 1,4-benzothiazene -2,3-diones, acetidinone thiazolidinone. *Indian academic science* (Chem. Science) 1990; 102 (4) :535- 540.

Mogilaiah K, Babu Rao R. Synthesized the indole [2',3':5, [1,2,4] -triazeno [4,3-alpha] [1,8]- naphthyridines and 3'- (3-phenyl-1, 8-naphthyridin- 2-ylamin) spiro- [3H-3,2'-thiazolidine] - 2,4'(1H) - diones as potential anti-bacterial agents.

Mohd Amir MS Y Khan, Zaman MS. Synthesized, characterized andhas shown biological activities of substituted oxadiazole, triazole, thiadiazole and4-thiazolidine derivatives. Indian JChemB2004;43(B):2189–2194.

MulwadVV, Choudhari BP. Synthesized the anti-microbial screening of N-[colemarin-6-ylamino] thiazolidine and spiro indolo- thiazolidino derivatives. Indian J Chem B 2005; 44 (B):1074-1078.

Raghuram Rao A, Rajan KS, Dev singh S, Bhagavan Raju M. (2001). Synthesized the H_1 anti-histaminic evaluation of 3-[N,N- (dialkyl amino) alkyl] -6-halo-2-phenyl-3,4 dihydroquinazoline-4(3H)-ones. *Indian J Chem B,* 40(B):813–816.

Reddy PSN, Manmahan Reddy, Pradap Reddy P. (2003). Synthesized new heterocycle, 1H-4-aryl [1,2,4]-oxadiazeno[5,4-b] quinozoline. *Indian J Chem B*;42(B):2119– 2120.
