Research Article

Synthesis, *in vitro* evaluation for anthelmintic and antimicrobial activity for the novel thiazolidine-4-one incorporate substituted chloro-quinoline

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Abstract

Objective: Helminthiases is also called infection caused by worms in intestinal reason and can spread to organs of human beings, which is an macro parasitic disease by contaminated ingestion of food and materials, these also decreases the immune power of body which can attack for bacterial or viral infections, an attempt is made to prepare some heterocyclic compounds which can use against to treat both disease causing pathogens in society. **Material and methods**: A new seven heterocyclic compound of 4-thiazolidinone is synthesized from substituted chloro quinoline contain imine Schiff's bases. The Schiff's compounds are obtain by condensing previously prepared H, F & OCH_3 substituted 2-chloro-3-formyl quinoline($Q_{1,2,3}$) by standard method with substituted aryl amine in rectified sprit under catalytic acid, which referred as Schiff's base (azomethine)(Qam_{1-7}). These Schiff's base compounds further cyclized by treated with mercapto acetic acid in DMF using metal catalyst by conventional way to obtain the desired compounds of 4-thiazolidinone incorporate quinolines($Q_{TZ\,1-7}$) as desired. The reaction time varies by performing TLC. All the obtain compounds are characterized and evaluated for *in vitro* anthelmintic and antimicrobial which describe in studies. **Results:** The data obtain of the synthesized some novel series of 4-thiazolidinone contain chloro quinoline confirms structure by FT-IR: C=N 1640-1620, C=O 1700-1640 (Thiazolidin-4-one), C-S 700-680 thiazolidinone. ^{1}H-NMR 2.59 s, 2H of CH_2 of thiazolidinone, 7.2-8.9 m, Aromatic group, 3.1 s, 3H of methoxy and Mass spectroscopy by EI for compounds. The values obtain by anthelmintic over *Pheretima Posthuma* Indian earth worms show the paralyzed and death time compared with standard Albendazole formulated drug, compound code $Q_{TZ-6,5,2\,and\,3}$ shows prominent activity and antimicrobial by MIC shows significant to moderate activity on bacterial and fungal strains. **Conclusion:** the novel 4-thiazolidinone contains quinoline and its substituent's shows significant activity against worms and microbial media.

Key words: Azomethine, quinoline, thiazolidin-4-one, anthelmintic and antimicrobial

Introduction

It is the challenging predicament in the field of medicine in treating infectious diseases in hospital based healthcare because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant. These resistant microorganisms cause infectious diseases which are considered as an important challenge to the medical community and need for an effective therapy has led to an increasing search for novel chemical entities which rule against these pathogens. Thiazolidin-4-one incorporated some bicyclic compounds, which belong to an important group of heterocyclic compounds, have been extensively explored for their application in the field of medicine. Some naturally occurring molecules containing thiazolidinone moiety showed important activities like antibiotic, immunosuppressive, antitumor, antifungal, anticonvulsant, COX-1 inhibitors, anti-tuberculosis, anti-inflammatory, anthelmintic and antihistaminic activity so on (Babaoglu et al., 2003). Importantly thiazolidine-4-ones containing β-lactam ring stops the bio-synthesis of p-glycone moiety which is needed for cell wall of bacterial organism. Mur-B

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enzyme is a unique target for antibacterial activity of thiazolidinone. Quinoline is a heterocyclic aromatic organic compound possessing nitrogen atom as part of the ring system (Srivastava et al., 2006), it forms an important key core units in a large number of pharmaceuticals, agrochemicals and in material science. By regularizing interest has been created in the chemistry of quinoline due to their wide spectrum of therapeutic activities like bactericidal, anti-HIV, antimalarial, antitumor, inhibitors of gastric (H+/K+)-ATPase, dihydroorotate dehydrogenase, 5-lipoxygenase, leukotriene-D4 receptor antagonist and anthelmintic (Benmohammed et al., 2014). In the present work a series of novel thiazolidi-4-ones are synthesized baring quinoline/substituted quinolines, to increase the efficacy of the pharmacological values over disease causing organism. A substituted of simple, fluoro and methoxy containing 2-chloro -3-formyl quinoline are prepared by versatile method using Vilsmeier hack reagent as per given in literature. These obtain compounds reacted with different aryl amine to give azomethine derivatives, further cyclized by condensing with thioglycolic acid in metal salt to get a desired compounds. Structural properties are studied and evaluated for antimicrobial and anthelmintic activity using standard models.

Material and methods

The chemicals and reagents used in the above titled work are self funded and purchased from Himedia, Fischer syntifics, Qualigens & Merck chemicals. The melting point for the compounds were determined by open capillary method which are incorrect, elemental analysis result obtain from free software Chem sketch ver.10, all the synthesized compounds are characterized and identified by FT-IR by KBr method using analytical technologies FT-IR spectrophotometer 2202. Some selected compounds were subjected to ^{1}H-NMR spectra data were recorded on Bruker 300 MHz in DMSO and Mass spectra by MS-EI for structural confirmation, and the compounds are evaluated for *in vitro* anthelmintic using Indian earth worm *Pheretima Posthuma* and antimicrobial activities (for bacteria and fungi) by using standard procedure with slight modification and the results are shown in the table no 2, 3 & 4.

Experimental work

General procedure for 2-chloro-3-formyl quinoline ($Q_{1,2,3}$)

A substituted Simple, fluoro and methoxy on 6th position of quinoline is done by previous established procedure (Balaji et al., 2012; Srivastava et al., 2005). Obtained compounds are recrystalised and its M.P are determined.

Synthesis of azomethine from substituted 2-cl-3-formyl quinoline (Qam_{1-7})

A equimolar concentration of simple/substituted quinolones (0.15M) is treated with substituted aryl amine (0.15M) is taken in a 250 ml round bottomed flask containing ethanol (30ml), the mixture was condensed on water bath. After 30 min a few drops of week acid was added as catalytic reagent and condensation was continued for 6-8 hrs (Balaji et al., 2014). The reaction mixture was cooled and poured into a beaker containing crushed ice and stirred rapidly to obtain the precipitate. The precipitate was filtered and washed with water and recrystalised by alcohol to obtain desired Schiff –base.

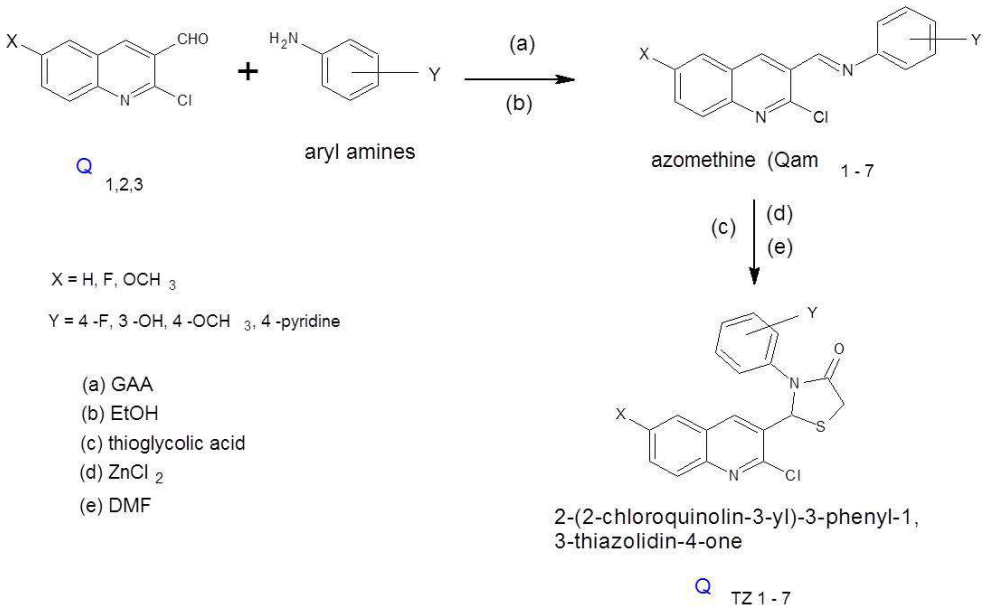

Figure 1. Synthesis of thiazolidine-4-one desired compound from azomethine ($Q_{TZ\ 1-7}$)

Table 1. Characteristic analytical data for synthesized compounds- substituted quinoline-3-carbaldehyde & azomethine contain quinolines

S.NO	C.C	Molecular formula	M.WT	% Yield	M.P ^{0}C ± 2	Calculated %						
						C	H	N	O	F	S	Cl
1	Q_1	$C_{10}H_6ClNO$	191.61	76	129	62.68	3.16	7.31	8.35	-	-	18.50
2	Q_2	$C_{10}H_5ClFNO$	209.60	80	220	57.30	2.40	6.68	7.63	9.06	-	16.91
3	Q_3	$C_{11}H_8ClNO_2$	221.63	79	148	59.61	3.64	6.32	14.44	-	-	16.00
4	Q_{am-1}	$C_{16}H_{10}ClFN_2$	284.71	56	132	67.50	3.54	9.84	-	6.67	-	12.45
5	Q_{am-2}	$C_{16}H_{11}ClN_2O$	282.72	62	216	67.97	3.92	9.91	5.66	-	-	12.54
6	Q_{am-3}	$C_{17}H_{13}ClN_2O$	296.75	50	155	68.81	4.42	9.44	5.39	-	-	11.95
7	Q_{am-4}	$C_{17}H_{12}ClFN_2O$	314.74	52	160	64.87	3.84	8.90	5.08	6.04	-	11.26
8	Q_{am-5}	$C_{16}H_{12}ClN_3O$	297.73	55	178	64.54	4.06	14.11	5.37	-	-	11.91
9	Q_{am-6}	$C_{17}H_{13}ClN_2O_2$	312.75	65	206	65.29	4.19	8.96	10.23	-	-	11.34
10	Q_{am-7}	$C_{17}H_{12}ClFN_2O$	314.74	60	158	64.87	3.84	8.90	5.08	6.04	-	11.26

Synthesis of thiazolidine-4-one desired compound from azomethine ($Q_{TZ\ 1-7}$)

Substituted azomethine (0.01M) was taken with (0.02M) mercapto acetic acid (thioglycolic acid) in a 40 ml of DMF all over taken in 250 ml round bottom flask. to this add anhydrous $ZnCl_2$ was added as catalyst and reflux the mixture on heating mantle for 8-12 hour (exact time was determined by TLC for different substituent's) with occasional shaking later cool the mixture poured into crushed ice to precipitate, collect the product filtered dried and recrystalised by proper solvent (Ilango et al., 2010).

Characterization data for thiazolidine-4-one

Q_{TZ-1}: 2-(2-chloroquinolin-3-yl)-3-(4-fluorophenyl)-1,3-thiazolidin-4-one

Mol formula: $C_{18}H_{12}ClFN_2OS$, M.Wt: 358.17, % yield 48, M.P (^{0}C) 220, IR (KBr cm^{-1}): C-H(Ar) =3080, C=C(Ar)=1580, C=N1635, C-Cl=755, C=O=1690, C-S=785, C-F=1158. H^1-NMR : 2.59 (s, 2H, -CH_2 of Thiazolidinone), 7.2 – 8.9 (m, 9 H, Ar-H), 6.2 (s, 1H, CH). MS (EI): m/z 358.6.

Q_{TZ-2}: 2-(2-chloroquinolin-3-yl)-3-(4-hydroxyphenyl)-1,3-thiazolidin-4-one

Mol formula:: $C_{18}H_{13}ClN_2O_2S$, M.Wt: 356.82 , % yield 52, M.P (^{0}C) 208, IR (KBr cm^{-1}): C-H (Ar) =3080, C=C (Ar)=1610, C=N=1640,C-Cl=780,C=O=1710,C-S=700,C-OH=3580. H^1-NMR : 2.62 (s, 2H, -$CH_2$of Thiazolidinone), 7.1-8.8 (m, 9 H, Ar-H), 6.7(s,1H,CH),13.45(s, 1H, OH). MS (EI): m/z 356.44.

Q_{TZ-3}: 2-(2-chloroquinolin-3-yl)-3-(4- methoxyphenyl)-1,3-thiazolidin-4-one

Mol formula:: $C_{19}H_{15}ClN_2O_2S$, M.Wt: 370.85 , % yield 42, M.P (^{0}C) 160, IR (KBr cm^{-1}): C-H(Ar) =3040, C=C(Ar)=1620, C=N=1600, C-Cl=830, C=O=1700, C-S=680, C-OCH_3= 2820.

Q_{TZ-4}: 2-(2-chloro-6-fluoroquinolin-3-yl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one

Mol formula:: $C_{19}H_{14}ClFN_2O_2S$, M.Wt: 388.84, % yield 40, M.P (^{0}C) 168, IR (KBr cm^{-1}): C-H(Ar) =3090, C=C(Ar)=1620, C=N=1640, C-Cl=1720, C=O=1690, C-S=680, C-OCH_3=2820, C-F=1140. H^1- NMR : 2.52 (s, 2H, -CH_2 of Thiazolidinone),7.2-8.7(m,8H, Ar-H), 6.77(s,1H,CH),3.0(s, 3H, OCH_3). MS (EI): m/z 387.55.

Q_{TZ-5}: 2-(2-chloro-6-methoxyquinolin-3-yl)-3- pyridin-4-yl-1,3-thiazolidin-4-one

Mol formula: $C_{18}H_{14}ClN_3O_2S$, M.Wt: 371.84, % yield 50, M.P (^{0}C) 220, IR (KBr cm^{-1}): (C-H(Ar)=3080, C=C(Ar)=1580, C=N=1635, C-Cl=840, C=O1685, C-S=785, C-OCH_3=1240.

Q_{TZ-6}: 2-(2-chloro-6-methoxyquinolin-3-yl)-3-(4-hydroxyphenyl)-1,3-thiazolidin-4-one

Mol formula: $C_{19}H_{15}ClN_2O_3S$, M.Wt: 386.85, % yield 46, M.P (^{0}C) 196, IR (KBr cm^{-1}): C-H(Ar)=3120, C=C(Ar)=1590, C=N=1620, C-Cl=710, C=O=1680, C-S=740, C-OH=3610. H^1- NMR : 2.56 (s, 2H, -CH_2 of Thiazolidinone), 7.15 – 8.86 (m, 8 H, Ar-H), 6.82 (s, 1H, CH), 3.45 (s, 3H, OCH_3), 12.3 (s, 1H, OH). MS (EI): 385.04.

Q_{TZ-7}: 2-(2-chloro-6-methoxyquinolin-3-yl)-3-(4-fluorophenyl)-1,3-thiazolidin-4-one

Mol formula: $C_{19}H_{14}ClFN_2O_2S$, M.Wt: 388.84, % yield 48, M.P (^{0}C) 165, IR (KBr cm^{-1}): (C-H(Ar)=3080, C=C(Ar)=1580, C=N=1650, C-Cl=820, C=O=1680, C-S=540, C-OCH_3=3610, C-F=1150.

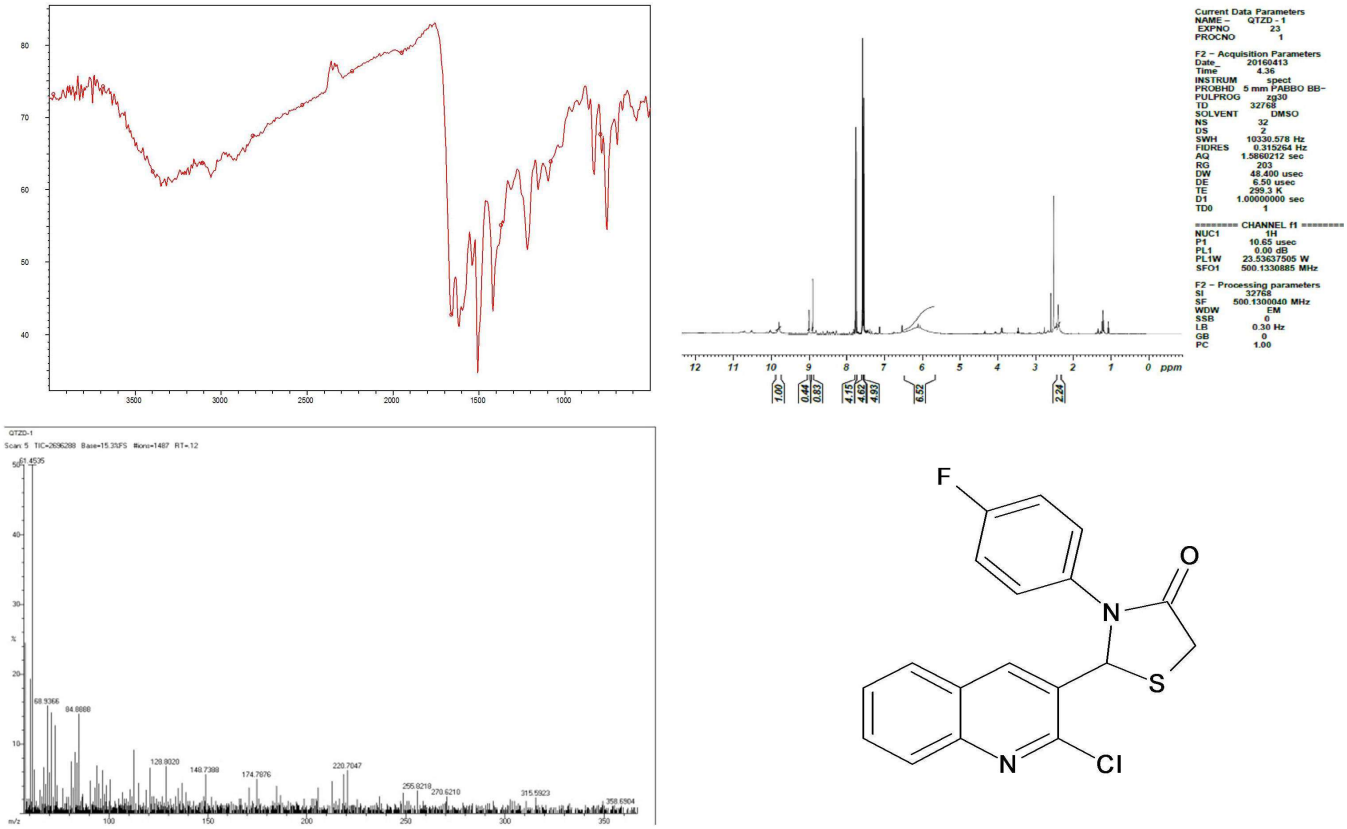

Figure 2. A Sample Spectra for the compound Q_{TZ-1} : 2-(2-chloroquinolin-3-yl)-3-(4-fluorophenyl)-1,3-thiazolidin-4-one

Antimicrobial activity by MIC Method

Minimum inhibitory concentration (MIC)

Minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation. MIC values can be determined by a number of standard test procedures. The most commonly employed methods are the tube dilution method and agar dilution methods. Serial dilutions are made of the products in bacterial/fungal broth. The test organisms are then added to the dilutions of the products, incubated, and scored for growth. This procedure is a standard assay for antimicrobials. Minimum inhibitory concentrations are important in diagnostic laboratories to confirm resistance of microorganisms to an antimicrobial agent and also to monitor the activity of new antimicrobial agents. An MIC is generally regarded as the most basic laboratory measurement of the activity of an antimicrobial agent against an organism. Clinically, the minimum inhibitory concentrations are used not only to determine the amount of antibiotic that the patient will receive but also the type of antibiotic used, which in turn lowers the opportunity for microbial resistance to specific antimicrobial agents.

Preparation of suspension of micro-organism

Transferring the microorganisms from the culture (*S. aureus, Bacillus subtilis, P.aeruginosa and E. coli)* to 5 ml of sterile normal saline (0.09 %) solution.

Determination of minimal inhibitory concentration (MIC)

The sterile test tubes containing 1 ml of sterile media were added with 1 ml of different serially diluted test samples. To these tubes, 0.1 ml of suspension of respective microorganism was added in normal saline and incubated at 37 ± 2^0 C for 24 hr. After 24 hr a loop full of sample was streaked in zigzag fashion over the agar medium in Petridis from the culture and this was incubated at 37 ± 2^0 C for 24 hr.

Then the lowest concentration of the sample that inhibited the microbial growth in the Petridis was determined and this is considered as MIC.

Anti-fungal activity

Preparation of suspension of micro-organism

The test organisms **(***Aspergillus flavus* and *Candida albicans)* were sub-cultured using potato dextrose agar medium. The tubes containing sterilized medium were inoculated with test fungi and after incubation at 25 °C for 48 hr and they were stored at 4 °C in a refrigerator.

Determination of minimal inhibitory concentration (MIC)

Table 2. Anti-bacterial activity by MIC (µg/ml)

S. No	Compound Code	*Staphylococcus aureus*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*
1	Q_{TZ-1}	12.5	25	12.5	50
2	Q_{TZ-2}	12.5	25	50	12.5
3	Q_{TZ-3}	25	25	25	50
4	Q_{TZ-4}	25	12.5	12.5	25
5	Q_{TZ-5}	25	25	50	25
6	Q_{TZ-6}	25	12.5	12.5	50
7	Q_{TZ-7}	25	12.5	12.5	12.5
8	Amoxicillin	1.56	3.12	3.12	3.12

The inoculums were prepared by taking a loopful of stock culture to about 100 ml of nutrient broth, in 250 ml clean and sterilized conical flasks. The flasks were incubated at 27 °C for 24 hr before use. The plates were kept undisturbed for at least two hours at room temperature to allow diffusion of the solution properly, into potato-dextrose-agar medium. Then the plates were incubated at 25 °C for 48 hr. The highest dilution showing at least 99 % inhibition zone is taken as MIC. The result of this is much affected by the size of the Inoculums. The experiments were performed in duplicate in order to minimize the errors.

Anthelmintic activity

The synthesized compounds are screened for Anthelmintic activity by using Mathew et al method and Indian adult earthworms (*Pheretima posthuma*). The earthworms (collected from the water logged areas of soil in and around Tiruchanoor, Tirupati) were washed with normal saline to remove all feacal materials.

Table 3. Antifungal activity by MIC (µg/ml)

Sl No	Compound Code	*Candida albicans*	*Aspergillus flavus*
1	Q_{TZ-1}	12.5	25
2	Q_{TZ-2}	12.5	12.5
3	Q_{TZ-3}	25	50
4	Q_{TZ-4}	12.5	12.5
5	Q_{TZ-5}	25	12.5
6	Q_{TZ-6}	50	25
7	Q_{TZ-7}	50	25
8	Griseofulvin	3.12	6.25

The earthworms in 4 - 5 cm in length and 0.1 - 0.2 cm in width were used for all experimental protocol. The earthworm resembles both anatomically and physiologically to the intestinal roundworm parasites of human beings, hence can be used to study anthelmintic activity.

Table 4. Anthelmintic activity of synthesized compounds

S.NO	Compounds code	% Concentration in w/v	Average time in minutes	
			Paralysis time	Death time
1	Control	0.9%	-	-
2	Albendazole	0.1%	38	44
		0.2%	30	36
		0.5%	22	24
3	Q_{TZ-1}	0.1%	43	45
		0.2%	49	62
		0.5%	52	54
4	Q_{TZ-2}	0.1%	13	22
		0.2%	10	27
		0.5%	40	58
5	Q_{TZ-3}	0.1%	35	39
		0.2%	21	29
		0.5%	24	32
6	Q_{TZ-4}	0.1%	39	43
		0.2%	27	29
		0.5%	19	21
7	Q_{TZ-5}	0.1%	35	38
		0.2%	26	28
		0.5%	22	26
8	Q_{TZ-6}	0.1%	33	37
		0.2%	25	27
		0.5%	21	22
9	Q_{TZ-7}	0.1%	41	44
		0.2%	32	34
		0.5%	33	35

Five earthworms of nearly equal size were placed in standard drug solution and test compounds solutions at room temperature. Normal saline used as control. The standard drug and test compounds were dissolved in minimum quantity of dimethyl sulfoxide (DMSO) and adjusted the volume up to 15 ml with normal saline solution to get the concentration of 0.1 % w/v, 0.2 % w/v and 0.5% w/v. Albendazole was used as a standard drug. The compounds were evaluated by the time taken for complete paralysis and death of earthworms. The mean lethal time for each test compound was recorded and compared with standard drug. The time taken by worms to become motionless was noted as paralysis time. To ascertain the death of the motionless worms were frequently applied with external stimuli, which stimulate and induce movement in the worms, if alive. The mean lethal time for paralysis and death of the earthworms for different test compounds and standard drug are tabulated in table.

Result and discussion

Chemistry

A novel series of thiazolid-4-one heterocyclic compounds incorporated with substituted quinoline moiety are prepared as per literature with little modification. The prepared substituted (simple, fluoro and methoxy on 6th position) of 2-chloro-3-formyl-6-substituted quinoline are made to react with different aryl amine in catalytic acid in ethanol to produce series of Schiff's base Q_{am1-7}. Later cyclization of this Schiff bases with thioglycolic acid in metal catalyst in DMF by conventional process to give a desired thiazolidine-4-one (2-(2-chloroquinolin-3-yl)-3-phenyl-1,3-thiazolidin-4-one) $Q_{TZ\ 1-7}$ with substitution are obtain and purified by recrystalization. All the obtained compounds are subjected to physical evaluation by M.P done by open capillary which are incorrect, all compounds are subjected to FT-IR by KBr pellet method for function group evaluation and selected compound with different functional moieties on surface are subjected to ^{1}H-NMR and Mass spectroscopy interpretation are shown in data.

Biological activity

All the above synthesized compounds are subjected to evaluate *In-vitro* antimicrobial and anthelmintic activity by standard procedure using standard drug as reference. Different bacterial strains like (*S. aureus, B. subtilis, P.aeruginosa and E. coli)* are pre-cultured as per guidelines and treated with prepared compounds. The compound $Q_{TZ-2,4,7}$ contain Fluoro, methoxy and hydroxy side chain shows significant antibacterial activity compared with standard drug amoxicillin rest of the compounds shows good to moderate. For the fungal (*Aspergillus flavus* and *Candida albicans)* the compound shows significant to moderate activity as compared to reference drug.

Anthelmintic property for the synthesized compounds are done using Indian earth worm *Pheretima Posthuma* the standard Albendazole and synthesized compounds are dissolved in suitable solvent and worms are placed in Petridis were the paralysis time and death time are noted which gives an result of good anthelmintic property. Compound $Q_{TZ\ -\ 4,5,6}$ shows good activity compared with standard.

Conclusion

The seven novel synthesized heterocyclic 4-thiazolidinone contained substituted quinoline which is obtained from 2-chloro-3-formyl quinoline condense with aryl amine in acidic catalyst to give series of azomethine compounds which further cyclized with thioglycolic acid in DMF by conventional process afford a very potent desired heterocyclic compounds, structure are identified by spectroscopic studies and its biological potency are determined by antimicrobial and anthelmintic properties lies significant activity, this makes us to extend our research work to synthesize some more novel heterocyclic compounds of thiazolidinone with different functional attachment in future.

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