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Synthesis of Quinoline Derivatives by Microwave Irradiation Method and Evaluation for Their Anti-Helminthic Activity

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Abstract: *The search for new antihelminthic drugs is an area of active investigation with the goal of developing novel drugs in order to overcome the phenomenon of drug resistance. It is well-known that the quinoline nucleus and its derivatives play a vital role in the design of an important class of wide spectrum antihelminthic agents. The chemical entities were synthesized by Iron powder, HCl, O-Nitro Benzaldehyde, Ethanol using novel methods like conventional method and Microwave irradiation methods. The best yields, less consumption of time and purity was observed by Microwave irradiation method. From the series of compounds synthesized from 5.21a to 5.21i, 5.21c, 5.21g, and 5.21h showed significant antihelminthic activity. Compound 5.21c showed 0.69 min for paralysis of worms and the death time was recorded to be 2.19 min at a concentration of 1mg/ml.*

Keyword: *conventional method, Microwave irradiation method, quinoline nucleus, antihelminthic activity.*

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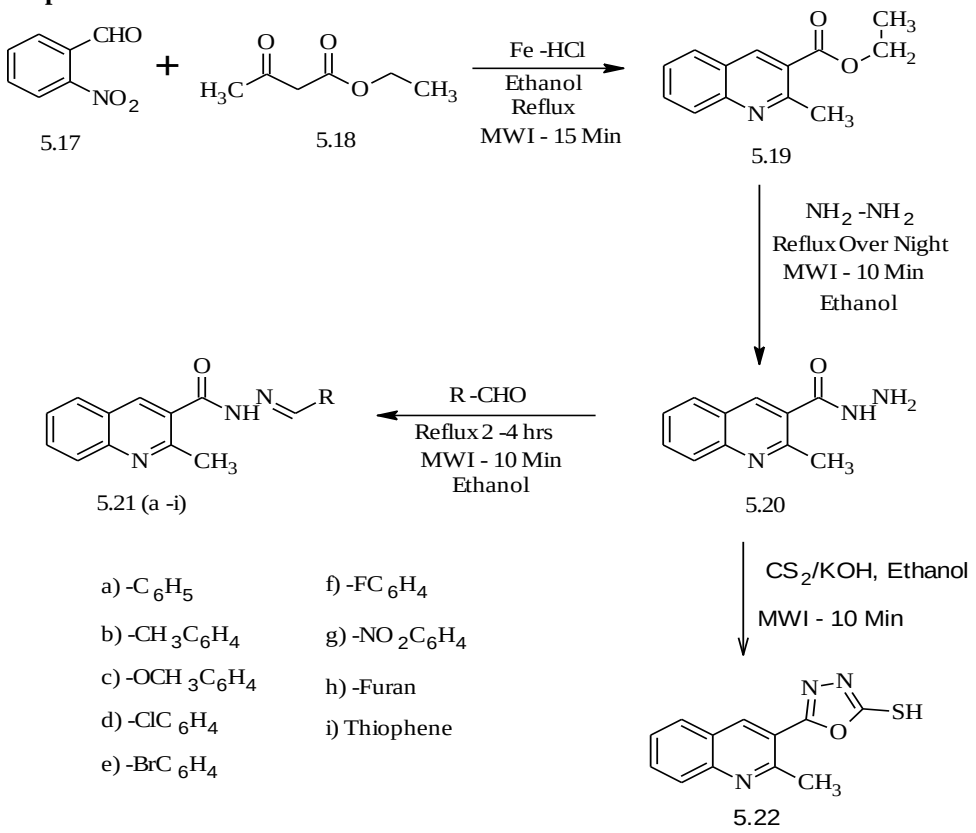
I. Introduction

Among the wide variety of heterocyclic compounds that have been explored for developing pharmaceutically important molecules, quinoline have played an important role in medicinal chemistry in last few decades. Quinoline ring is endowed with various activities, such as antituberculosis[1], antimalarial[2], anti-inflammatory[3], anticancer[4], antibiotic[5], antihypertensive[6], tyrokinase inhibiting agents[7]and anti-HIV[8]. Hydrazones are active pharmacophores which posses an azomethine —NHN=CH— proton constituting an important class of compounds for new drug development. They form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications that include antibacterial[9], antifungal[10]and anti-tumor activities[11].

II. Material and Methods

This study was carried out by using following chemicals Iron powder, HCl, *O*-Nitro Benzaldehyde, Ethanol, *β*-Ketoester, Ethylacetoacetate, Thin Layer Chromatography Plates, Saturated Sodium Bicarbonate Solution ($NaHCO_3$), anhydrous Na_2SO_4 from Vijay Enterprises, Shop Number:149/A, Saidabad, Hyderabad. Petridishes, Piperazine citrate, Normal Saline, and 2-methyl-N'-methylidene quinoline-3-carbohydrazides.

Experimental procedure:



Synthesis of ethyl 2-methylquinoline-3-carboxylate(5.19):

Iron powder (4mmol) and 0.1M HCl (0.05mmol) were sequentially added to a solution of an *o*-nitro benzaldehyde in ethanol and the resulting mixture was stirred vigorously at 95 ^{0}C (oil bath) temperature while reaction mixture was monitored by TLC. On completion of the reaction, the β-ketoester was added and the reaction mixture was refluxed for 6hrs. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature; Ethanol was removed under reduced pressure, diluted with Ethylacetate and filtered through the celite pad. The filtrate was neutralized with saturated sodium bicarbonate solution ($NaHCO_3$), washed with water two times, and the aqueous phase was extracted with ethylacetate. The organic phase was dried by using anhydrous Na_2SO_4, filtered and solvent was removed under reduced pressure. The crude material recrystallized from hexane and the colored impurities were removed by activated charcoal treatment.

Microwave irradiation[12]:

Iron powder (4mmol) and 0.1M HCl (0.05mmol) were sequentially added to a solution of an *o*-nitro benzaldehyde in ethanol and the resulting mixture was irradiated at 95 ^{0}C while reaction mixture was monitored by TLC. On completion of the reaction, the β-ketoester was added and the reaction mixture was again irradiated under microwave for 15 Minutes. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature, EtOH was removed under reduced pressure, diluted with ethylacetate and filtered through the celite pad. The filtrate was neutralized with saturated sodium bicarbonate solution ($NaHCO_3$), washed with water two times, and the aqueous phase was extracted with ethylacetate. The organic phase was dried by using anhydrous Na_2SO_4, filtered and solvent was removed under reduced pressure. The crude material recrystallized from hexane and the colored impurities were removed by activated charcoal treatment.

Synthesis of 2-methylquinoline-3-carbohydrazide(5.20):

Quinoline ester (1eq) was dissolved in absolute ethanol (5ml) and excess amount of hydrazine hydrate (99%, 3eq) was added to the reaction mixture and refluxed for overnight. Completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature; white crystals were separated out

from reaction mixture. Then crystals were filtered, and washed with cold ethanol to get a pure compound. These crystals have enough purity to proceed for further step.

Microwave irradiation:

Quinoline ester (1eq) was dissolved in absolute ethanol (5ml) and excess amount of hydrazine hydrate (99%, 3eq) was added to the reaction mixture and irradiated for 10 minutes. Completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature; white crystals were separated out from reaction mixture. Then crystals were filtered, and washed with cold ethanol to get a pure compound. These crystals have enough purity to proceed for further step.

Synthesis of derivatives of 2-methylquinoline-3-carbohydrazide: (5.21a-i)

To a solution of Quinoline Hydrazide (1 mol) in absolute ethanol (5ml) and then corresponding arylaldehydes (1 mol) were added and refluxed for requisite time. Completion of reaction was monitored by TLC. The reaction mixture was cooled to room temperature, solid thus obtained was filtered and washed with cold ethanol to obtain pure product.

Microwave irradiation:

To a solution of Quinoline Hydrazide (1 mol) in absolute ethanol (5ml) and then corresponding arylaldehydes (1 mol) were added and irradiated for 10 minutes. Completion of reaction was monitored by TLC. The reaction mixture was cooled to room temperature, solid thus obtained was filtered and washed with cold ethanol to obtain pure product

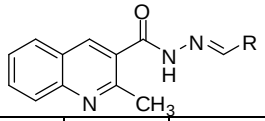
Synthesis of 5-(2-methylquinolin-3-yl)-1,3,4-oxadiazole-2-thiol: (5.22)

A mixture of Quinoline Hydrazide (0.1) moles, KOH(0.1moles), CS_2(0.1moles) & ethanol (20ml) was heated under reflux until the evaluation of hydrogen sulphide ceased. The reaction mixture was cooled to room temperature & poured in to ice cold water (100ml). It was neutralized with dillute HCl. The ppt solid was filtered, washed with water & dried product was recrystallized from ethanol.

Microwave irradiation:

A mixture of Quinoline Hydrazide (0.1) moles, KOH(0.1moles), CS_2(0.1moles) & ethanol (20ml) was irradiated until the evaluation of hydrogen sulphide ceased. The reaction mixture was cooled to room temperature & poured in to ice cold water (100ml). It was neutralized with dilute HCl. The ppt solid was filtered, washed with water & dried product was recrystallized from ethanol.

Physical data:



Product	R	Mol. formula	M. Wt	Conventional Yield (%)	MWI Yield (%)	M.P (^{0}C)
5.21a	C_6H_5-	$C_{18}H_{15}N_3O$	289	92.3	96.9	182-184
5.21b	4-CH_3-C_6H_4-	$C_{19}H_{17}N_3O$	303	89.1	94.5	204-206
5.21c	4-OCH_3-C_6H_4-	$C_{19}H_{17}N_3O_2$	319	90.2	97	170-172
5.21d	4-F-C_6H_4-	$C_{18}H_{14}N_3OF$	307	91.1	95.3	180-183
5.21e	4-Cl-C_6H_4-	$C_{18}H_{14}N_3OCl$	323	89.5	93.7	210-212
5.21f	4-Br-C_6H_4-	$C_{18}H_{14}N_3OBr$	368	88.9	96.6	215-217
5.21g	4-NO_2-C_6H_4	$C_{18}H_{14}N_4O_3$	334	92.4	98.4	200-202
5.21h	2 - Furanyl	$C_{16}H_{13}N_3O_2$	279	93.6	97.5	202-204
5.21i	2 - Thiophenyl	$C_{16}H_{13}N_3OS$	295	91.7	98	230-232
5.22	Oxadiazole	$C_{12}H_9N_3OS$	243	89.5	95.8	245-247

Anthelminthic activity:

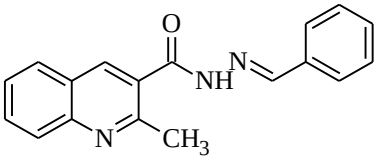
The increasing prevalence of helminth parasites those are resistant to conventional anthelminthics have been the spur for different research programs exploring alternative approaches to parasite control.

Method:

The synthesized compounds were evaluated for anthelmintic activity in *Pheretimaposthuma* (earth worms) of nearly equal size (6 ± 1 cm). *Pheretimaposthuma* is used due to its anatomical and physiological resemblance with the intestinal roundworm parasite of human being. The worms were acclimatized to the laboratory condition before experimentation. The earth worms were divided into groups of six earth worms in each. Piperazine citrate diluted with normal saline solution to obtained 0.1, 0.2, 0.5 and 1% m/*V* served as standard and poured into petri dishes. Test solutions were prepared in minimal quantity of ethanol and diluted to prepare four concentrations *i.e.,* 0.1, 0.2, 0.5 and 1% m/*V* for each compound. Normal saline serves as control. Six earth worms were nearly equal size (6 ± 1 cm) are taken for each concentration and placed in petriplates at room temperature. The time taken for complete paralysis and death are recorded. The mean paralysis time and lethal time for each sample was calculated (each reading were taken in a triplicate). The time taken for worms to become motionless was noted as paralysis time and to ascertain death, each worm was frequently applied with external stimuli which stimulates and induce movement in the worms, if alive.

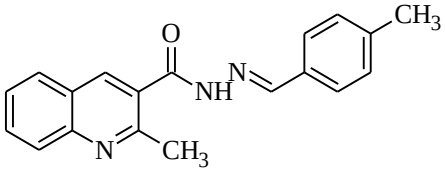
III. Results and discussion

2-methyl-*N*'-[(*E*)-phenylmethylidene]quinoline-3-carbohydrazide: 5.21a



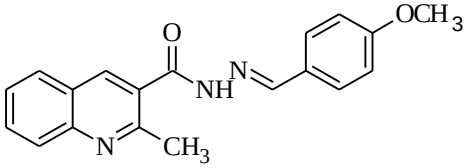
Molecular Formula: $C_{18}H_{15}N_3O$; M.Wt: 289; M.P: 182-184^{0}C**;** I.R: 3192(NH), 2967(CH) 1721(C=O). ^{1}H NMR: 11.69 (1H, s), 8.29 & 8.15 (1H, s, Cis-trans conformer), 8.17-7.47 (1H, m), 7.88-7.61 (3H, m), 7.57-7.47 (1H, q), 7.42-7.32 (2H, m), 7.24 (2H, d), 2.85 & 2.73 (3H, s, Cis-trans conformer); ^{13}C NMR:163.41, 157.21, 147.51, 147.58, 136.82, 134.12, 132.41, 131.14, 131.51, 130.12, 130.19, 130.21, 129.61, 128.91, 128.96, 127.90, 127.12 & 22.93; Mass (ESI):m/z: 290$(M+H)^+$;

2-methyl-*N*'-[(*E*)-(4-methylphenyl)methylidene]quinoline-3-carbohydrazide: 5.21b



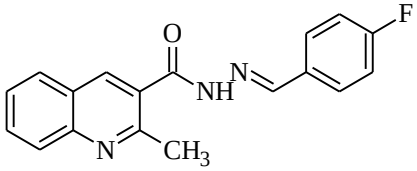
Molecular Formula: $C_{19}H_{17}N_3O$; MWt: 303; M.P: 204-206^{0}C**;** ; I.R: 3215(NH), 1651(C=O). ^{1}H NMR : 11.76 & 11.68 (1H, s, Cis-trans conformers), 8.30 & 8.25 (1H, s, Cis-trans conformer), 7.98 (1H, d),7.91-7.60 (4H, m), 7.53 (1H ,t), 7.22 (2H, t), 7.03 (1H, d), 2.83(3H, s, Cis-trans Conformer), 2.40-2.29 (3H, s, Cis-trans Conformer); ^{13}C NMR:163.46, 157.32, 147.98, 148.25, 136.76, 134.81, 132.57, 131.63, 131.51, 130.44, 130.37, 130.29,129.24, 129.11, 129.07, 128.54, 127.94, 22.96 & 21.28; Mass (ESI):m/z: 304$(M+H)^+$, 330$(M+Na)^+$.

***N*'-[(*E*)-(4-methoxyphenyl)methylidene]-2-methylquinoline-3-carbohydrazide: 5.21c**



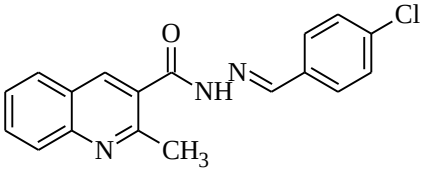
Molecular Formula :$C_{19}H_{17}N_3O_2$:Formula Weight ; 319; M.P;172-172^{0}C; I.R: 3464(NH), 1666(C=O) ^{1}H NMR : 8.30 & 8.24 (1H, s, Cis-trans Conformer), 7.99 (1H, d), 7.93-7.64 (4H, m), 7.55 (1H, t), 7.29 (1H, d), 6.91(1H, d),6.74 (1H, d), 3.85 & 3.75 (3H, s, Cis-trans Conformer), 2.83 & 2.70 (3H, s, Cis-trans Confomer). ^{13}C NMR:163.85,157.53,147.90,148.22,136.32,134.54,132.87,131.54, 131.26, 130.77, 130.69, 130.19,129.79,129.77,128.61,127.38, 55.17 22.96 & 21.23 Mass (ESI):m/z: 320$(M+H)^+$, 342$(M+Na)^+$.

***N*'-[(*E*)-(4-fluorophenyl)methylidene]-2-methylquinoline-3-carbohydrazide: 5.21d**



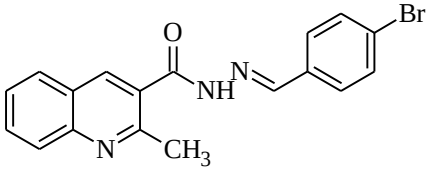
Molecular Formula: $C_{18}H_{14}N_3OF$; MWt: 307; M.P: 180-183^{0}C**;** I.R: 3467(NH), 1692(C=O), ^{1}H NMR : 11.83 &11.82(1H, s, Cis-trans Conformer), 8.10 & 8.13 (1H, s, Cis-trans Conformer), 8.09-7.92 (3H, m), 7.88-7.93 (2H, m), 7.56-7.65(2H, m), 7.29 (1H, d), 7.24 (1H, d), 2.96 & 2.59(3H, s, Cis-trans Conformer), ^{13}C NMR:163.29, 157.18, 148.41, 147.51, 131.30, 134.2, 132.51, 131.24, 131.64, 131.45, 130.26, 130.05, 130.22, 126.84, 126.15, 126.54, 126.03 & 22.2, Mass (ESI):m/z: 308$(M+H)^+$, 330$(M+Na)^+$, $)^+$.

***N*'-[(*E*)-(4-chlorophenyl)methylidene]-2-methylquinoline-3-carbohydrazide: 5.21e**



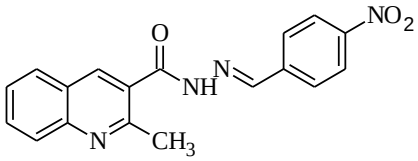
Molecular Formula: $C_{18}H_{14}N_3OCl$; MWt: 323; M.P: 210-212^{0}C**;** I.R: 3184(NH), 2957(CH) 1684(C=O) ^{1}H NMR : 8.35 & 8.29 (1H, s, Cis-trans Conformer), 8.16 & 8.05 (1H, s, Cis-trans Conformer), 8.01-7.94 (2H, m), 7.80-7.69 (2H, t), 7.60-7.49 (1H, t), 7.44-7.21 (3H, m), 2.81 & 2.68 (3H, s, Cis-trans Conformer). ^{13}C NMR: 163.19, 152.22, 148.84, 147.60, 134.41, 134.22, 132.15, 131.51, 131.41, 131.75, 130.44, 130.31, 130.27, 126.92, 126.22, 126.98, 126.03 & 22.5; Mass (ESI):m/z: 324$(M+H)^+$, 326$(M+2)^+$.

***N*'-[(*E*)-(4-bromophenyl)methylidene]-2-methylquinoline-3-carbohydrazide: 5.21f**



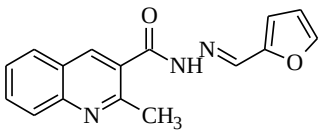
Molecular Formula: $C_{18}H_{14}N_3OBr$; MWt: 368; M.P: 215-217^{0}C**;** I.R: 3184(NH), 1654(C=O). ^{1}H NMR : 11.85 & 11.87 (1H, s, Cis-trans Conformer), 8.33 & 8.28 (1H, s, Cis-trans Conformer), 8.07-7.82 (3H, m), 7.80-7.63 (2H, m), 7.61-7.47 (2H, m), 7.36 (1H, d), 7.25 (1H, d), 2.82 & 2.69 (3H, s, Cis-trans Conformer). ^{13}C NMR: 163.25, 157.11, 147.55, 148.28, 136.24, 134.35, 132.47, 131.62, 131.47, 130.26, 130.17, 130.22, 129.11, 129.07, 128.14, 115.94, 115.84 & 22.31; Mass (ESI):m/z: 368$(M+H)^+$, 370$(M+2)^+$.

***N*'-[(*E*)-(4-bromophenyl)methylidene]-2-methylquinoline-3-carbohydrazide: 5.21g**



Molecular Formula: $C_{18}H_{14}N_4O_3$; MWt: 334; M.P: 200-202 ^{0}C**;** I.R: 3179(NH), 2941(CH) 1694(C=O), ^{1}H NMR : 11.82&11.84 (1H, s, Cis-trans Conformer), 8.11 & 8.15 (1H, s, Cis-trans Conformer), 8.08-7.91 (3H, m), 7.86-7.91 (2H, m), 7.55-7.64 (2H, m), 7.27 (1H, d), 7.22 (1H, d), 2.90 & 2.57(3H, s, Cis-trans Conformer), ^{13}C NMR: 163.22, 157.13, 150.41, 147.27, 136.38, 134.26, 132.45,131.09, 131.18, 131.59, 130.10, 130.14, 130.31, 126.93, 126.29, 126.14, 126.05 & 22.93 Mass (ESI):m/z: 335$(M+H)^+$.

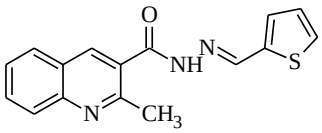
***N*'-[(*E*)-furan-2-ylmethylidene]-2-methylquinoline-3-carbohydrazide: 5.21h**



Molecular Formula: $C_{16}H_{13}N_3O_2$; MWt: 279; M.P: 202-204^{0}C**;** I.R: 3194(NH), 2965(CH) 1697(C=O),^{1}H NMR: 11.71 & 11.63 (1H, s, Cis-trans Confrmer), 8.27 & 8.24 (1H, s, Cis-trans Conformer), 7.99 (1H, t), 7.84 (1H, t), 7.73 (1H, q), 6.86 (1H, s), 6.51(1H, s). ^{13}C NMR: 163.74, 156.41, 149.74, 146.38, 137.41, 134.84, 134.98,

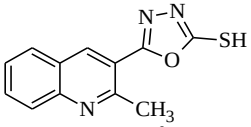
132.17, 132.81, 131.43, 131.25, 131.12, 130.97, 119.71, 113.46 & 22.94; Mass (ESI):m/z: 280$(M+H)^+$, 302$(M+Na)^+$.

***N*'-[(*E*)-furan-2-ylmethylidene]-2-methylquinoline-3-carbohydrazide: 5.21i**



Molecular Formula: $C_{16}H_{13}N_3OS$; MWt: 295; M.P: 230-232 ^{0}C**;** I.R: 3189(NH), 2954(CH) 1751(C=O) ^{1}H NMR : 11.84 & 11.74 (1H, s, Cis-trans Conformer), 8.53 & 8.30 (1H, s, Cis-trans conformer), 8.18 (1H, d), 8.02-7.67 (3H ,m), 7.58-6.91 (4H, m), 2.81 & 2.70 (3H, s, Cis-trans Conformer); ^{13}C NMR: 163.72, 156.40, 141.72, 140.35, 137.40, 134.81, 134.96, 132.12, 132.80, 131.41, 131.22, 131.11, 130.92, 119.68, 113.31 & 22.54; Mass (ESI):m/z: 296$(M+H)^+$, 318$(M+Na)^+$.

***N*'-[(*E*)-furan-2-ylmethylidene]-2-methylquinoline-3-carbohydrazide: 5.22**



Molecular Formula: $C_{12}H_9N_3OS$; MWt: 243; M.P: 245-247^{0}C**;** I.R: 3184(NH), 2957(CH) 1684(C=O). ^{1}H NMR : 8.21 (1H, s,), 8.06 (1H, d,), 8.01 (1H, d), 7.83 (H, t), 7.67 (1H, t), 3.21(3H, s,) 3.04(1H,s).^{13}C NMR: 165.52, 156.96, 146.75, 136.35, 134.41, 132.81, 131.12, 130.64, 130.12, 129.54, 127.98 & 22.54; Mass (ESI):m/z: 244 $(M+H)^+$.

IV. Result

Anthelmintic Activity Of 2-Methyl-*N*'-[(*E*)-Phenylmethylidene]Quinoline-3-Carbohydrazide Derivatives

S.No	Compound	Conc. %	Time (min, Mean ± SEM)	
			For paralysis	For death
1	5.21a	0.1	2.74 ± 0.59	4.65 ± 0.81
		0.2	2.46 ± 0.62	4.01 ± 0.28
		0.5	1.99 ± 0.25	3.72 ± 0.90
		1.0	1.19 ± 0.85	2.69 ± 0.57
2	5.21b	0.1	2.03 ± 0.09	4.42 ± 0.20
		0.2	1.49 ± 0.07	4.27 ± 0.23
		0.5	1.25 ± 0.11	3.45 ± 0.19
		1.0	1.26 ± 0.52	3.28 ± 0.04
3	5.21c	0.1	1.46 ± 0.16	4.21 ± 0.21
		0.2	1.25 ± 0.08	4.01 ± 0.24
		0.5	1.09 ± 0.71	3.34 ± 0.23
		1.0	0.69 ± 0.69	2.19 ± 0.11
4	5.21d	0.1	3.52 ± 0.05	4.60 ± 0.23
		0.2	2.38 ± 0.90	4.38 ± 0.17
		0.5	1.90± 0.96	3.40 ± 0.22
		1.0	1.06 ± 0.04	2.58 ± 0.74
5	5.21e	0.1	3.86 ± 0.21	5.00 ± 0.40
		0.2	2.32 ± 0.40	4.69 ± 0.72
		0.5	1.18 ± 0.52	4.14 ± 0.14
		1.0	1.01 ± 0.14	3.04 ± 0.81
6	5.21f	0.1	1.96 ± 0.44	4.51 ± 0.90
		0.2	1.59 ± 0.95	4.29 ± 0.17
		0.5	1.22± 0.11	3.47 ± 0.84
		1.0	1.09 ± 0.88	2.50 ± 0.93
7	5.21g	0.1	1.89 ± 0.64	5.00 ± 0.19
		0.2	1.45 ± 0.60	4.06 ± 0.81
		0.5	1.27 ± 0.51	4.23 ± 0.41
		1.0	0.96 ± 0.46	3.29 ± 0.30
8	5.21h	0.1	1.99 ± 0.44	4.67 ± 0.22
		0.2	1.50 ± 0.71	4.56 ± 0.47
		0.5	1.21 ± 0.47	3.81 ± 0.51
		1.0	0.99± 0.55	2.42 ± 0.94
9	5.21i	0.1	2.64 ± 0.29	5.80 ± 0.43
		0.2	2.36 ± 0.18	5.21 ± 0.49
		0.5	2.01 ± 0.17	4.75 ± 0.86
		1.0	1.13 ± 0.09	3.47 ± 0.86
Piperazine citrate (Standard drug)		0.1	1.36 ± 0.06	4.11 ± 0.21

	0.2	1.21 ± 0.09	4.02 ± 0.24
	0.5	1.05 ± 0.03	3.58 ± 0.23
	1.0	0.54 ± 0.02	2.16 ± 0.03

V. Discussion

Among the series of compounds synthesized from 5.21a to 5.21i, 5.21c, 5.21g, 5.21h showed significant antihelminthic activity. Compound 5.21c showed 0.69 min for paralysis of worms and the death time was recorded to be 2.19 min at a concentration of 1mg/ml. Compound 5.21g showed 0.96min for paralysis of worms and the death time was recorded to be 3.29 min at a concentration of 1mg/ml. Compound 5.21h showed 0.99 min for paralysis of worms and the death time was recorded to be 2.42 min at a concentration of 1mg/ml.

VI. Conclusion

In this study we have shown the importance of quinolines as antihelminthic chemical entities. The proposed quinolines were synthesized and evaluated for their antihelminthic activity. Synthesized by conventional and Microwave irradiation methods and found the significant results. The new chemical entities were characterized by different spectroscopic methods like I.R, ^{1}H NMR, Mass Spectroscopy methods. Among the series of compounds synthesized from 5.21a to 5.21i, 5.21c, 5.21g, 5.21h showed significant antihelminthic activity. Compound 5.21c showed 0.69 min for paralysis of worms and the death time was recorded to be 2.19 min at a concentration of 1mg/ml.

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