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# Synthesis of Some New 2-Mercapto/Hydrizino 5, 6, 7, 8 - Tetrahydro Quinazoline Derivatives as *In-Vitro* Anthelimentic Agents

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## ABSTRACT
A new series of substituted 5, 6, 7, 8 tetrahydro quinazoline derivative has been synthesized from a mixture of methyl/ethylacetoacetate with different substituted aromatic/ hetero aromatic aldehydes. Then treated with aminoguanidines / thiourea afforded 2-hydrizino substituted 5, 6, 7, 8-tetrahydro quinazoline ($D_{1-8}$)/ 2-mercapto substituted 5, 6, 7, 8-tetrahydro quinazoline derivatives ($E_{1-8}$). The structures of newly synthesized compounds were confirmed by spectral data (IR, $H^1$NMR, $C^{13}$NMR, Mass spectra and Elemental analysis).The synthesized compounds were also evaluated for their anthelimentic activity using earth worms of nearly equal size (8 cm±1) were selected randomly for present study and Albendazole was used as reference standard. The compounds which contains Cl and F groups substituted at *Para* position on phenyl ring at $C_5$ of substituted 5, 6, 7, 8 tetrahydro quinazoline derivatives showed good activity when compared with reference standard.

**Keywords:** Tetrahydro quinazoline, anthelimentic activity, 2-mercapto/r-hydrizinyl and Albendazole (ALB)

## 1. INTRODUCTION
Gastrointestinal parasites create a serious threat to the production of livestock in developing nations. As per WHO, only few drugs are frequently used in the treatment of helminthes in human beings. Helminthes parasite infections are global problems with serious social and economic repercussions in developing countries. Some type of dangerous helminthes infections like filariasis has only a few therapeutic modalities at present. The universal requirement on heterocyclic compounds for their potential activities against microorganisms and significance in the pharmaceutical field prompted us to synthesize pyrimidines and pyrazolines from cyclic keto esters. Cyclohex-2-enones are useful in the synthesis of organic compounds [1-5]. Synthesis of cyclohex-2-enones involves Knoevenagel condensation of acetylacetone or ethyl acetoacetate with aromatic aldehydes in the presences of methylamine in ethanol, yielded cyclic β-keto esters. We have found that the quinqzoline and condensed quinazoline derivatives are found to exhibit potent biological[6-11] and pharmaceutical activities. In view of the above and in a continuation of our interest in the development of quinazoline/quinazolinone chemistry. We have synthesized new 2-mercapto/hydrizino substituted 5, 6, 7, 8 tetrahydro quinazoline derivatives for anthelimentic activity.

## 2. MATERIALS AND METHODS

### 2.1 *Preparation of 3-aryl-2, 4-biscarbethoxy-5-hydroxy-5-methylcyclohexanones ($C_{1-8}$)*
All the compounds $C_{1-8}$ were prepared by using the procedure of Pandiarajan et al[12]. A mixture of methyl/ethylacetoacetate (A) (100 mmoles), aromatic benzaldehyde (B) (50 mmoles) and methylamine (50 mmoles) in ethanol (50 mL) was warmed on a water bath for about 10 min. The reaction mixture was kept overnight for one / two days respectively. The separated solid was filtered and it was purified by recrystallisation from ethanol.

### 2.2 *Preparation of $D_{1-8}$ & $E_{1-8}$*
Compound $C_{1-8}$ (10 mmoles) was dissolved in ethanol (3mL) and after addition of hydrazine hydrate (15 mmoles) the reaction mixture was heated under reflux for 2h. Then the mixture was cooled and poured into crushed ice, and the precipitate was filtered off, dried, and recrystallized from ethanol.

## 3. EXPERIMENTAL PROCEDURE
Melting points of the newly synthesized compounds were determined in open capillary tubes and were uncorrected. IR Spectra were recorded on a Perkin – Elmer $BXF_1$, FT-IR spectrophotometer using KBr disc and the values expressed in $cm^{-1}$. $H^1$NMR Spectra were recorded on a Bruker AMX, 400 MHz, using TMS as an internal standard and the values are expressed in ppm. Mass Spectrum was recorded on Agilent 1100 ESI- Mass (turbo spray) spectrophotometer. C H N analysis was carried out on Carlo Erba 1108 Elemental analyzer. Homogeneity of the compounds was checked by TLC on silica gel plates.

### 3.1 *4 - ethoxy - 2 - hydrazinyl - 7 - hydroxyl - 7 - methyl - 5, 6, 7, 8 - tetrahydro - 5 - (p -tolyl) - quinazoline - 6 - ethylcarboxylate ($D_1$).*
m.p. 98-100$^0$C, yield 82%, Rf 0.61; IR (KBr, Cm-1) 3400 (NH, Str), 1560 (C=N, Str), 1170 (C-O-C, Str), 1690 (C=O of $COOC_2H_5$,Str ), 3090 (OH, Str), 2810 (C-H, Str); $H^1$ NMR (δ ppm) 5.34 (2H,s,H-N-H), 10.15 (1H,s,N-

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H), 4.72 (1H, s, OH at $C_7$), 1.06 (3H, s, Me at $C_7$), 1.28 (3H, s, Me of $COOC_2H_5$), 3.41 (2H, d, $CH_2$ of $COOC_2H_5$), 2.85 (3H, s, Me of $OC_2H_5$), 3.26 (2H, d, $CH_2$ of $OC_2H_5$), 7.01- 7.26 (4H, m, Ar-H ), 4.63 (1H, s, 5Ha ), 3.31 (1H, s, 6Ha), 1.98 (3H, s, Ar-$CH_3$ at $C_5$), 5.08 (2H, s, 8 Ha & 8 He ); $C^{13}$NMR (δ ppm): $C_2$-139.89, $C_4$-138.73, $C_5$ – 60.56, $C_6$-76.74, $C_7$-77.37, $C_8$-60.48, $C_9$-136.22, $C_{10}$-129.23, $CH_2$ of $OC_2H_5$ at $C_4$-54.26, $CH_3$ of $OC_2H_5$ at $C_4$-21.01, C=O of $COOC_2H_5$ at $C_6$ -172.95, $CH_2$ of $COOC_2H_5$ at $C_6$-53.84, $CH_3$ of $COOC_2H_5$ at $C_6$-21.84, $CH_3$ at C8-16.45, Ar- $CH_3$ at $C_5$ -31.03, aromatic carbons: 1'-129.11, 128.80,128.97,127.50,127.36, 126.94; Mass (*m/z*) 400 (M+,18%), 359 (100%); anal. calcd(found) 63.00 (63.02), 6.98 (7.02), 14.06 (13.98) for $C_{21}H_{28}O_4N_4$.

**3.2** ***4 - ethoxy - 2 - hydrazinyl - 7 - hydroxyl - 7 - methyl - 5, 6, 7, 8 - tetrahydro - 5 -phenylquinazoline - 6 - ethylcarboxylate ($D_2$).***

m.p. 192-194$^0$C, yield 91%, Rf 0.65; IR (KBr, Cm-1) 3420 (NH, Str), 1480 (C=N,str), 1220 (C-O-C, str), 1665 (C=O of $COOC_2H_5$, str), 3030 (OH, Str), 2870 (C-H, Str); $H^1$ NMR (δ ppm) 5.85 (2H, s, H-N-H), 9.18 (1H, s, N-H), 4.17 (1H, s,OH at $C_7$), 1.05 (3H, s, Me at $C_7$), 2.46 (3H, s, Me of $COOC_2H_5$), 3.86 (2H, d, $CH_2$ of $COOC_2H_5$), 2.67 (2H, s,), 3.82 (2H, d, $CH_2$ $OC_2H_5$), 7.102- 7.260 (5H, m, Ar-H), 4.62 (1H, s, 5Ha ), 3.34 (1H, s, 6Ha) , 5.24 (2H, s, 8 Ha & 8 He ); Mass (*m/z*) 386 (M+,08%); anal.calcd(found) 62.17 (62.36), 6.70 (6.90), 14.50 (14.26) for $C_{20}H_{26}O_4N_4$.

**3.3** ***4 - ethoxy - 2 - hydrazinyl - 7 - hydroxyl - 7 - methyl - 5, 6, 7, 8 - tetrahydro - 5 - (p-chlorophenyl) - quinazoline - 6 - ethylcarboxylate ($D_3$).***

m.p. 122-124$^0$C, yield 84%, Rf 0.71; IR (KBr, Cm-1) 3420 (NH, str), 1460 (C=N, str), 1230 (C-O-C, str), 1670 (C=O of $COOC_2H_5$, str ), 3240 (OH, str), 2825 (C-H, str), 780 (C-Cl, str) ; $H^1$ NMR (δ ppm) 5.40 (2H,s,H-N-H), 10.41 (1H,s,N-H), 4.10 (1H, s, OH at $C_7$), 1.11 (3H, s, Me at $C_7$ ), 2.17 (3H, s, Me of $COOC_2H_5$), 3.88 (2H, d, $CH_2$ of $COOC_2H_5$), 2.32 (3H,s, Me of $OC_2H_5$), 3.32 (2H, d, $CH_2$ of $OC_2H_5$), 7.03- 7.29 ( 4H, m, Ar-H ), 4.28 ( 1H, s, 5Ha ), 3.96 ( 1H, s, 6Ha), 5.46 (2H, s, 8Ha & 8H e ). Mass (*m/z*) 420.5 (M+, 09%); anal. calcd (found) 57.07 (57.28), 5.94 (6.12), 13.31 (13.16) for $C_{20}H_{25}O_4N_4Cl$

**3.4** ***4 - ethoxy - 2 - hydrazinyl - 7 - hydroxyl -7 - methyl - 5, 6, 7, 8 - tetrahydro - 5 - (4 -fluorophenyl) quinazoline - 6 - ethylcarboxylate ($D_4$).***

m.p. 100-102$^0$C, yield 45%, Rf 0.72; IR (KBr, Cm-1): 3355 (NH, Str), 1490 (C=N, Str), 1265 (C-O-C, Str), 1655 (C=O of $COOC_2H_5$,Str ), 3060 (OH, Str), 2845 (C-H, Str), 1080 (C-F, str); $H^1$ NMR (δ ppm) 5.20 (2H ,s, H-N-H), 10.05 (1H, s, N-H), 4.86 (1H, s, OH at $C_7$ ),1.27 (3H, s, Me at $C_7$ ), 1.64 ( 3H, s, Me of $COOC_2H_5$ ), 3.18 ( 2H, d, $CH_2$ of $COOC_2H_5$ ), 2.99 ( 3H, s Me of $OC_2H_5$), 3.42 ( 2H, d, $CH_2$ of $OC_2H_5$ ) , 7.00- 7.26 ( 4H, m , Ar-H ), 4.78 ( 1H, s, 5Ha ), 3.26 ( 1H, s, 6Ha ), 5.02 (2H, s, 8Ha & 8He ); Mass (*m/z*) 404 (M+, 12%); anal. calcd (found) 59.40 (59.53), 6.18 (6.33), 13.86 (13.78) for $C_{20}H_{25}O_4N_4F$.

**3.5** ***4 - methoxy - 7 - methyl - 2 - hydraziny - 7 - hydroxy - 5, 6, 7, 8 - tetrahydro - 5 - (p - tolyl) phenylquinazoline - 6 - methylcarboxylate ($D_5$).***

m.p. 112-114$^0$C, yield 65%, Rf 0.63; IR (KBr, Cm-1) 3450 (NH, Str), 1485 (C=N, Str), 1245 (C-O-C, Str), 1660 (C=O of $COOCH_3$,Str ), 3230 (OH, Str), 2890 (C-H, Str); $H^1$ NMR (δ ppm) 5.40 (2H, s, H-N-H) , 10.06 (1H ,s, N-H) , 4.70 (1H , s, OH at $C_7$ ) , 2.05 (3H ,s, Me at $C_7$), 1.60 ( 3H, s, Me of $COOCH_3$ ), 1.89 ( 3H, s, Me of $OCH_3$), 2.43 (3H, s, Ar-$CH_3$ at $C_5$) 7.01- 7.33 ( 4H, M , Ar-H ) , 3.42 ( 1H, s, 5Ha ), 3.00 ( 1H ,s, 6Ha ), 5.51 (2H, s, 8Ha & 8He ); Mass (*m/z*) 372 (M+, 11%); anal.calcd (found) 61.29 (61.46), 6.45 (6.52), 15.05 (15.08) for $C_{19}H_{24}O_4N_4$

**3.6** ***4 - methoxy - 7 - methyl - 2 - hydraziny - 7 - hydroxy - 5, 6, 7, 8 - tetrahydro - 5 -phenylquinazoline - 6 - methylcarboxylate ($D_6$).***

m.p. 170-172$^0$C, yield 63%, Rf 0.75; IR (KBr, Cm-1) 3335 (NH, Str), 1485 (C=N, Str), 1185 (C-O-C, Str), 1655 (C=O of $COOCH_3$,Str ), 3060 (OH, Str), 2880 (C-H, Str); $H^1$ NMR (δ ppm) 5.24 (2H, s, H-N-H), 9.22 (1H,s,N-H), 4.56 (1H, s, OH at $C_7$), 1.25 (3H, s , Me at $C_7$), 1.60 (3H, s, Me of $COOCH_3$), 1.89 (3H,s, Me of $OCH_3$), 7.14- 7.39 (4H,m,Ar-H) , 3.46 (1H, s,5Ha) , 3.01 ( 1H,s,6Ha) , 4.92 (2H, s, 8Ha & 8He ); Mass (*m/z*) 358 (M+, 22%); anal.calcd(found) 60.97 (61.08), 6.14 (6.23), 15.60 (15.58) for $C_{18}H_{22}O_4N_4$

**3.7** ***4 - methoxy - 7 - methyl - 2 - hydrazinyl - 7 - hydroxy - 5, 6, 7, 8 - tetrahydro - 5 - (4 -chlorophenyl) quinazoline - 6 - methylcarboxylate ($D_7$).***

m.p. 96-98$^0$C, yield 66%, Rf 0.61; IR (KBr, Cm-1) 3379 (NH, Str), 1489 (C=N, Str), 1295 (C-O-C, Str), 1676 (C=O of $COOCH_3$,Str ), 3185 (OH, Str), 2876 (C-H, Str), 816 (C-Cl, str); $H^1$ NMR (δ ppm) 5.91 (2H, s, H-N-H), 9.09 (1H, s, N-H), 4.81 (1H, s, OH at $C_7$), 0.96 (3H, s, Me at $C_7$), 2.60 (3H, s, Me of $COOCH_3$), 1.37 (3H, s, Me of $OCH_3$), 7.06- 7.31 (3H, m, Ar-H ), 3.52 (1H, s, 5Ha) , 2.97 ( 1H, s, 6Ha) , 5.36 (1H, s, 8Ha&8He); Mass (*m/z*) 392 (M+, 10%); anal.calcd(found) 55.03 (55.06), 5.35 (5.54), 14.26 (14.15) for $C_{18}H_{21}O_4N_4Cl$

**3.8** ***4 - methoxy - 7 - methyl - 2 - hydrazinyl - 7 - hydroxy - 5, 6, 7, 8 – tetrahydro - 5 - (4 -florophenyl) quinazoline - 6 - methylcarboxylate ($D_8$).***
m.p. 136-138$^0$C, yield 58%, Rf 0.42; IR (KBr, Cm-1) 3353 (NH, str), 1495 (C=N, str), 1279 (C-O-C, str), 1657 (C=O of $COOCH_3$, str ), 3224 (OH, str), 2842 (C-H, str), 1076 (C-F, str) ; $H^1$ NMR (δ ppm) : 5.72 (2H, s, H-N-H), 10.03 (1H, s, N-H), 4.34 (1H, s, OH at $C_7$), 1.17 (3H, s,-Me at $C_7$), 2.68 (3H, s, Me of $COOCH_3$), 1.25 (3H, s, Me of $OCH_3$), 7.06- 7.31 (3H, m, Ar-H ), 3.64 (1H, s, 5Ha), 2.86 ( 1H, s, 6Ha), 5.62 (2H, s, 8Ha&8He); Mass (*m/z*) 376 (M+, 05%); anal.calcd (found) 57.44 (57.66), 6.11 (6.24), 14.08 (13.95) for $C_{18}H_{23}O_4N_4F$

**3.9** ***7 - hydroxy - 2 - mercapto - 4 - methoxy - 7 – methyl - 5, 6, 7, 8 – tetrahydro – 5 - (p - tolyl) quinazoline - 6 - ethylcarboxylate ($E_1$).***
m.p. 252-254$^0$C, yield 78%, Rf 0.66; IR (KBr, Cm-1) 1263 (C-O-C, str), 1523 (C=N, str), 3063 (OH, str), 1667 (C=O of $COOC_2H_5$,str), 1139 (SH, str); $H^1$ NMR (δ ppm) 3.32 (1H, s, S-H), 2.81(3H, s, Me at $C_7$), 4.42 (1H, s, OH at $C_7$), 1.56 (3H, s, Me of $COOC_2H_5$), 3.86 (2H, d, $CH_2$ of $COOC_2H_5$), 1.64 (3H, s, Me of O $C_2H_5$), 3.40 (2H, d, $CH_2$ of O $C_2H_5$), 2.12 (3H, s, Ar-$CH_3$ at $C_5$), 7.08-7.26 (4H, m, Ar-H), 4.45 (1H, s, 5Ha), 3.16 (1H, s, 6Ha) 4.62 (2H, s, 8Ha&8He); Mass (*m/z*) 402 (M+, 15%); anal.calcd(found) 62.68 (62.74), 6.46 (6.66), 6.96 (6.54) for $C_{21}H_{26}O_4N_2S$

**3.10** ***7 - hydroxy - 2 - mercapto - 4 - methoxy - 7 – methyl - 5, 6, 7, 8 - tetra hydro - 5 -phenylquinazoline - 6 - ethylcarboxylate ($E_2$).***
m.p. 220-222$^0$C, yield 68%, Rf: 0.69; IR (KBr, Cm-1) 3265 (NH, str), 1260 (C-O-C, str), 1546 (C=N, str), 3037 (OH, str), 1675 (C=O of $COOC_2H_5$, str), 1143 (SH, str); $H^1$ NMR (δ ppm) : 3.03 (1H, s, SH), 2.95 (3H, s, Me at $C_7$), 4.48 (1H,s,OH at $C_7$), 1.25 (3H, s, Me of $COOC_2H_5$), 3.46 (2H, d, $CH_2$ of $COOC_2H_5$), 1.70 (3H, s, Me of $OC_2H_5$), 3.26 (2H, d, $CH_2$ of O $C_2H_5$), 7.08-7.26 (4H, m, Ar-H), 3.75 (1H, s, 5Ha), 3.30 (1H, s, 6Ha) 4.79 (2H, s, 8Ha&8He); Mass (*m/z*) 388 (M+, 19%); anal.calcd(found) 61.85 (62.02), 6.18 (6.22), 7.21 (7.12) for $C_{20}H_{24}O_4N_2S$

**3.11** ***7 - hydroxy - 2 - mercapto - 4 - methoxy - 7 - methyl - 5, 6, 7, 8 - tetrahydro - 5 - (p -chlorophenyl ) quinazoline - 6 - ethylcarboxylate ($E_3$).***
m.p. 196-198$^0$C, yield 78%, Rf 0.69; IR (KBr, Cm-1) 1190 (C-O-C, str), 1546 (C=N, str), 3376 (OH, str), 1646 (C=O of $COOC_2H_5$, str), 1146 (SH, str), 763 (C-Cl, str); $H^1$ NMR (δ ppm) 3.24 (1H, s, S-H), 2.95 (3H, s, Me at $C_7$), 4.69 (1H, s, OH at $C_7$), 1.43 (3H, s, Me of $COOC_2H_5$), 3.14 (2H, d, $CH_2$ of $COOC_2H_5$), 1.75 (3H, s, Me of $OC_2H_5$), 3.02 (2H, d, $CH_2$ of $OC_2H_5$) 7.04 -7.20 (4H, m, Ar-H), 4.75 (1H, s, 5Ha), 3.06 (1H, s, 6Ha) 4.70 (2H, s, 8Ha&8He); Mass (*m/z*) 422 (M+, 16%); anal.calcd(found) 56.80 (56.96), 5.44 (5.48), 6.62 (6.56) for $C_{20}H_{23}O_4N_2SCl$

**3.12** ***7 - hydroxy - 2 - mercapto - 4 - methoxy - 7 - methyl - 5, 6, 7, 8 - tetrahedro - 5 - (p -fluorophenyl) quinazoline - 6 - ethylcarboxylate ($E_4$).***
m.p. 262-264$^0$C, yield 54%, Rf 0.63; IR (KBr, Cm-1) 1242 (C-O-C, str), 1567 (C=N, str), 3235 (OH, str), 1665 (C=O of $COOC_2H_5$, str), 1215 (SH, str), 1054 (C-F, str); $H^1$ NMR (δ ppm) 3.27 (1H, s, SH), 2.67 (3H, s, $CH_3$ at $C_7$), 4.41 (1H, s ,OH at $C_7$), 1.56 (3H, s, Me of $COOC_2H_5$), 3.81 (2H, d, $CH_2$ of $COOC_2H_5$) 1.70 (3H, s, Me of O $C_2H_5$), 3.34 (2H, d, $CH_2$ of $OC_2H_5$), 7.03- 7.26 (4H, m, Ar-H), 4.57 (1H, s, 5Ha), 3.41 (1H, s, 6Ha) 5.04 (2H, s, 8Ha&8He); Mass (*m/z*) 406 (M+, 10%) anal.calcd(found) 59.11 (59.16), 5.66 (5.69), 6.89 (6.79) for $C_{20}H_{23}O_4N_2SF$

**3.13** ***7 - hydroxy - 2 - mercapto - 4 - methoxy - 7 - methyl - 5, 6, 7, 8 - tetrahydro - 5 - (p -tolyl) quinazoline - 6 - methylcarboxylate ($E_5$).***
m.p. 244-246$^0$C, yield 52%, Rf 0.67; IR (KBr, Cm-1) 1260 (C-O-C, str), 1543 (C=N, str), 3268 (OH, str), 1656 (C=O of $COOCH_3$, str), 1232 (SH, str); $H^1$ NMR (δ ppm) 3.23 (1H, s, SH), 2.91(3H, s, Me at $C_7$), 4.72 (1H, s, OH at $C_7$), 1.66 (3H, s, Me of $COOCH_3$), 1.47 (3H, s, Me of $OCH_3$), 7.26 (4H, m, Ar-H), 2.24 (3H, s, Ar-Me at $C_5$), 1.47 (1H, s, 5Ha), 3.06 (1H, s, 6Ha), 5.67 (2H, s, 8Ha&8He); Mass (*m/z*) 374 (M+, 20%); anal.calcd(found) 60.90 (60.99), 5.88 (6.11), 7.47 (7.49) for $C_{19}H_{22}O_4N_2S$

**3.14** ***7 - hydroxy - 2 - mercapto - 4 - methoxy - 7 - methyl - 5, 6, 7, 8 - tetrahydro - 5 -phenylquinazoline - 6 - methylcarboxylate ($E_6$).***
m.p. 232-234$^0$C, yield 84%, Rf 0.67; IR (KBr, Cm-1) 1247 (C-O-C, str), 1530 (C=N, str), 3356 (OH, str), 1667 (C=O of $COOCH_3$, str), 1236 (SH, str); $H^1$ NMR (δ ppm) 3.32 (1H, s, SH), 2.95 (3H, s, Me at $C_7$), 2.41 (1H, s, OH at $C_7$), 1.25 (3H, s, Me of $COOCH_3$), 1.70 (3H, s, Me of $OCH_3$), 7.26 (4H, m, Ar-H), 4.05 (1H, s, 5Ha), 4.30 (1H, s, 6Ha) 4.90 (2H, s, 8Ha&8He); Mass (*m/z*) 360 (M+, 12%); anal.calcd(found) 60.00 (60.02), 5.50 (5.58), 7.70 (7.42) for $C_{18}H_{20}O_4N_2S$

**3.15** ***7 - hydroxy - 2 - mercapto - 4 - methoxy - 7 - methyl - 5, 6, 7, 8 - tetrahydro - 5 - (p -chlorophenyl) quinazolin - 6 - methylcarboxylate ($E_7$).***

m.p. 148-150$^0$C, yield 72%, Rf 0.62; IR (KBr, Cm-1) 1267 (C-O-C, str), 1543 (C=N, str), 3237 (OH, str), 1693 (C=O of $COOCH_3$, str), 1198 (SH, str), 784 (C-Cl, str); $H^1$ NMR (δ ppm) 3.15 (1H, s, SH), 2.25 (3H, s, Me at $C_7$), 2.12 (1H, s, OH at $C_7$), 1.56 (3H, s, Me of $COOCH_3$) ,1.04 (3H, s, Me of $OCH_3$), 7.60 (4H, m, Ar-H), 4.25 (1H, s, 5Ha), 4.06 (1H, s, 6Ha) 4.82 (2H, s, 8Ha&8He); Mass (*m/z*) 394 (M+, 08%) anal.calcd(found) 54.75 (54.81), 4.81 (4.86), 7.09 (7.02) for $C_{18}H_{19}O_4N_2SCl$

### 3.16 *7 - hydroxy - 2 - mercapto - 4 - methoxy - 7 - methyl - 5, 6, 7, 8 - tetrahydro - 5 - (p -florophenyl) quinazolin - 6 - methylcarboxylate ($E_8$).*

m.p. 162-164$^0$C, yield 68%, Rf 0.45; IR (KBr, Cm-1) 1285 (C-O-C, str), 1545 (C=N, str), 3167 (OH, str), 1697 (C=O of $COOCH_3$ str), 1236 (SH, str), 1064 (C-F, str) ; $H^1$ NMR (δ ppm) 3.03 (1H, s, SH), 2.05 (3H, s, Me at $C_7$), 2.36 (1H, s, OH at $C_7$), 1.40 (3H, s, Me of $COOCH_3$), 1.62 (3H, s, Me of $OCH_3$), 7.18 (4H, m, Ar-H), 4.15 (1H, s, 5Ha), 4.56 (1H, s, 6Ha) 5.09 (2H, s, 8Ha&8He); Mass (*m/z*) 378 (M+, 13%); anal.calcd(found) 57.14 (57.40), 5.02 (5.31), 7.40 (7.36) for $C_{18}H_{19}O_4N_2SF$

### 3.17 *Experimental animals Collection*[13-14]

Indian adult earthworm (*P. Posthuma)* were collected from Guntur near Amaravathi road fields area, Andhra Pradesh, India, were used to study. The collected earthworms were, washed with normal saline to remove all faecal matter. The earthworms of 8 cm±1 in length and 1.5-2 cm in width were used for all experimental protocol. The earthworm's resembled the intestinal round worm parasites of human beings both anatomically and physiologically and hence where used to study the anthelimentic activity.

### 3.18 *Evaluation of Anthelmintic activity*[15]

The synthesized compounds were screened for anthelimentic activity. Earth worms of nearly equal size 8 cm±1 were selected randomly for present study. The earth worms were acclimatized to the laboratory condition before experimentation. The earthworms were divided into three groups of six earth worms each. Six earthworms of nearly equal size were placed in standard drug solution and test compound's solutions at room temperature. Normal saline used as control. Standard drug and test compounds 10mg, 50mg and 100mg were dissolved in minimum quantity of dimethyl formamide (DMF) and adjusted the volume up to 15 ml with normal saline solution. 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.

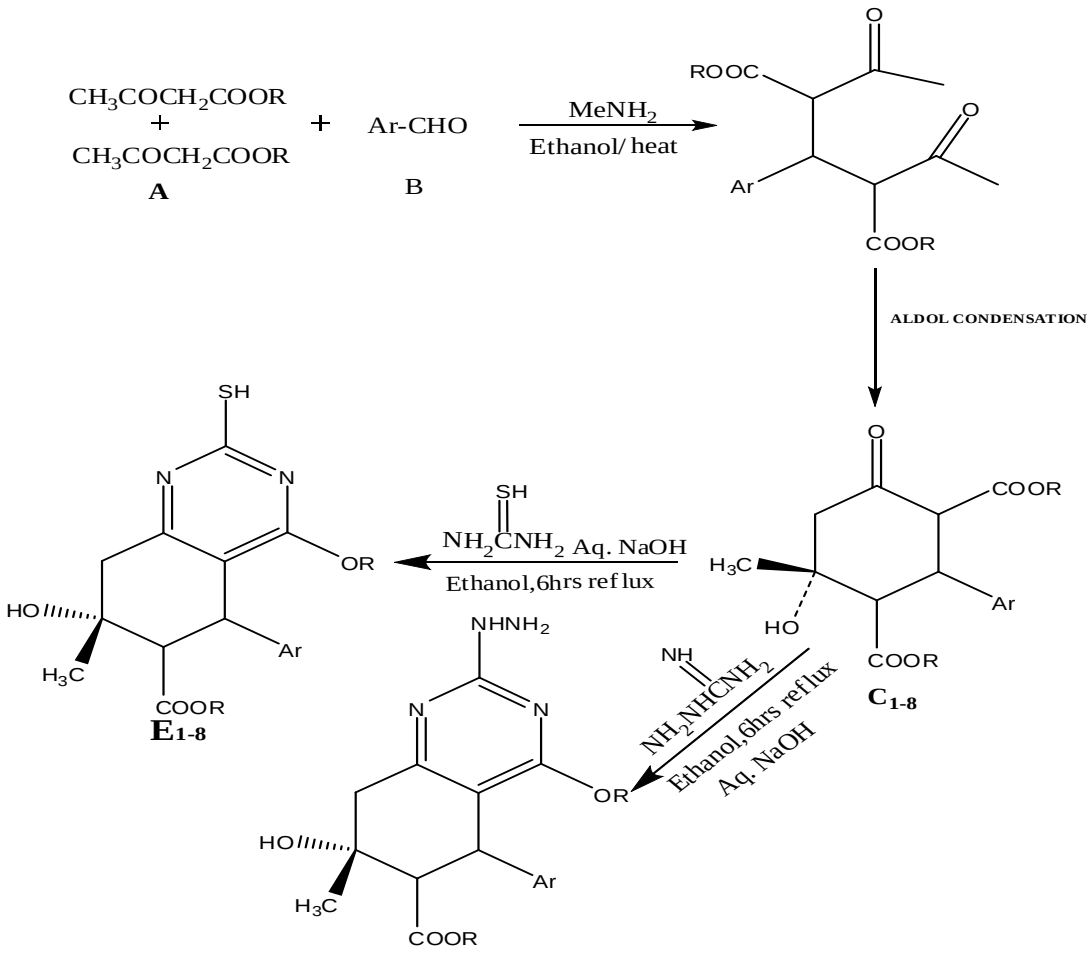
### 3.19 *Statistical Analysis*

Results were expressed as mean+SEM. statistical significance was determined by one-way analysis of variance (ANOVA) followed by Dunnet's test with the level of significance at $p < 0.01$ and $p < 0.001$.

## 4. RESULTS AND DISCUSSION

### 4.1 *Chemistry*

The series of heterocyclic $D_{1-8}$ & $E_{1-8}$ were newly synthesized by the reaction of $C_{1-8}$ with appropriate hydrazine hydrate & thiourea, after cyclization as presented in scheme-I. The IR, $H^1$NMR, $C^{13}$NMR, Mass & Elemental analysis for the newly synthesized compounds are in accordance with the assigned structures. The IR ($cm^{-1}$) spectrum of compounds in $D_{1-8}$ series showed the stretching bands of NH group at 3335-3450 respectively. The IR ($cm^{-1}$) spectrum of compounds in $E_{1-8}$ series showed the stretching bands of SH group at 1150-1250 respectively. The presence of NH group for $D_{1-8}$ & the presence of SH group for $E_{1-8}$ series provides a strong evidence for the condensation & also confirms the formation of 2-mercapto/ hydrizinyl 5, 6, 7, 8 - tetrahydro quinazoline derivatives. The $H^1$NMR (ppm) spectra of $D_{1-8}$ & $E_{1-8}$ and their corresponding derivatives have been recorded in $CDCl_3$. In $D_{1-8}$ series the $NH_2$ chemical shift appears at δ 5.2 - 5.9 for two (2*H*) protons and NH chemical shift appears at δ 9.0 - 10.5 for one (1*H*) proton respectively. In $E_{1-8}$ series the SH chemical shift appears at δ 3.0 - 3.5 for one (1*H*) proton respectively. The presence of NH and $NH_2$ chemical shift in the proton NMR spectra of final compounds confirms the hydrizinyl protons at $C_2$ position of 5, 6, 7, 8 tetrahydro quinazoline derivatives in $D_{1-8}$ series. The presence of SH chemical shift in $H^1$ NMR spectra of final compounds confirms at $C_2$ position of 5, 6, 7, 8 tetrahydro quinazoline derivatives in $E_{1-8}$ series.




| Entry | Ar | R |
|---|---|---|
| $D_1$ & $E_1$ | *p*-tolyl | $-C_2H_5$ |
| $D_2$ & $E_2$ | phenyl | $-C_2H_5$ |
| $D_3$ & $E_3$ | *p*-chloro | $-C_2H_5$ |
| $D_4$ & $E_4$ | *p*-floro | $-C_2H_5$ |
| $D_5$ & $E_5$ | *p*-tolyl | $-CH_3$ |
| $D_6$ & $E_6$ | phenyl | $-CH_3$ |
| $D_7$ & $E_7$ | *p*-chloro | $-CH_3$ |
| $D_8$ & $E_8$ | *p*-floro | $-CH_3$ |

**Scheme-1**

### 4.2 *Anthelimintic activity*

All the newly synthesized compounds screened for their anthelimentic activity. The observed results shown in Table-1. Among all the screened compounds some of the compounds showed moderate to considerable activity and particularly compounds $D_3$, $D_4$, $D_7$, $D_8$ & $E_3$, $E_4$, $E_7$ and $E_8$ have enhanced activity when compared to reference standard Albendazole due to the presence of chlorine and fluorine at *para* position on C-5 phenyl ring at minimal dose of 10mg/mL. At the concentration of 10mg/ml $D_3$, $D_4$, $D_7$, $D_8$ & $E_3$, $E_4$, $E_7$ and $E_8$ exhibited their good activity ($P < 0.001$) for time taken to paralysis and death when compared to standard Albendazole at 10mg/ml while increasing the concentration at 50mg/mL and 100mg/mL the compounds showed considerable activity ($P < 0.01$) by reducing the paralysis and death time when compared to standard.

## 5. CONCLUSION

The objective of this research work has to investigate anthelmintic activity of novel series of 2-substituted 5, 6, 7, 8 tetra hydro quinazolines prepared by the reaction of key intermediate $C_{1-8}$ with hydrazine hydrate and thiourea. The results of the anthelmintic activity of $D_{1-8}$ and $E_{1-8}$ series showed moderate enhancement of activity .The compounds $D_3$, $D_4$, $D_7$, $D_8$ & $E_3$, $E_4$, $E_7$ and $E_8$ emerged as the most active compound in exhibiting anthelmintic activity and rest of the compounds are having no significant activity when compared with the reference standard. Hence these series would be developed by as a novel class of anthelimentic agents. However further structural modifications is planned to increase the activity.

**Table-1:** Anthelimintic activity of synthesized compounds ($D_{1-8}$ & $E_{1-8}$)

| Time taken for paralysis and Death | | | | | | |
|---|---|---|---|---|---|---|
| | Paralysis time (min) | | | Death time (min) | | |
| **Entry** | **10mg/ml** | **50mg/ml** | **100mg/ml** | **10mg/ml** | **50mg/ml** | **100mg/ml** |
| **$D_1$** | 35.83 ± 1.537 | 56.83 ± 0.703 | 75.00 ± 4.280 | 34.16 ± 0.307 | 53.67 ± 2.076 | 74.16 ± 0.542 |
| **$D_2$** | 45.33 ± 1.308 | 67.16 ± 0.746 | 82.25 ± 0.250 | 48.83 ± 2.210 | 55.83 ± 0.870 | 67.33 ± 0.760 |
| **$D_3$** | 25.33 ± 1.174*** | 32.50 ± 0.500 | 48.50 ± 0.428 | 19.33 ± 1.202*** | 30.00 ± 3.055 | 45.00 ± 0.365 |
| **$D_4$** | 24.23 ± 0.980*** | 35.44 ± 1.820 | 49.55 ± 0.563 | 20.67 ± 0.550*** | 32.83 ± 1.187 | 52.44 ± 0.870 |
| **$D_5$** | 43.56 ± 0.650 | 51.35 ± 1.085 | 60.00 ± 0.987 | 39.88 ± 1.156 | 51.00 ± 1.054 | 70.36 ± 0.683 |
| **$D_6$** | 40.00 ± 0.447 | 52.33 ± 1.874 | 64.33 ± 0.210 | 40.56 ± 1.080 | 56.83 ± 1.270 | 74.83 ± 0.307 |
| **$D_7$** | 27.67 ± 2.028** | 39.66 ± 0.330 | 44.83 ± 0.307 | 20.33 ± 1.745** | 34.67 ± 1.783 | 48.90 ± 0.447 |
| **$D_8$** | 25.36 ± 1.067** | 40.50 ± 0.619 | 48.83 ± 0.317 | 21.50 ± 1.607** | 38.67 ± 0.802 | 51.17 ± 0.872 |
| **$E_1$** | 34.83 ± 1.400 | 41.50 ± 2.094 | 54.33 ± 0.210 | 32.67 ± 1.308 | 45.33 ± 1.687 | 56.50 ± 0.428 |
| **$E_2$** | 36.83 ± 2.380 | 42.17 ± 0.833 | 56.83 ± 0.600 | 38.00 ± 1.028 | 48.50 ± 0.619 | 62.16 ± 0.307 |
| **$E_3$** | 29.98 ± 2.078** | 34.30 ± 1.080 | 47.80 ± 0.109 | 21.55 ± 1.210** | 35.16 ± 0.912 | 52.87 ± 0.507 |
| **$E_4$** | 26.00 ± 1.930** | 36.83 ± 0.401 | 52.00 ± 0.258 | 23.83 ± 1.515** | 38.00 ± 1.125 | 53.66 ± 0.210 |
| **$E_5$** | 39.67 ± 0.557 | 49.16 ± 0.401 | 64.83 ± 0.307 | 46.47 ± 1.667 | 63.33 ± 6.009 | 78.50 ± 0.562 |
| **$E_6$** | 42.00 ± 0.447 | 56.33 ± 0.557 | 63.83 ± 0.307 | 32.17 ± 1.014 | 51.50 ± 0.806 | 75.00 ± 4.282 |
| **$E_7$** | 28.67 ± 0.666** | 29.50 ± 1.258 | 39.33 ± 0.333 | 19.67 ± 0.614*** | 38.33 ± 2.789 | 54.66 ± 0.494 |
| **$E_8$** | 27.50 ± 1.360** | 35.17 ± 1.447 | 45.00 ± 0.365 | 20.50 ± 0.763** | 39.50 ± 3.500 | 60.67± 3.333 |
| **ALB** | 24.17 ± 1.558 | - | - | 18.50 ± 0.763 | - | - |
| **Control** | - | - | - | - | - | - |

All determinations were done in triplicate and results are expressed as Mean ± SEM. P value was calculated by comparing with control by one-way ANNOVA. Control worms were alive up to 24 hrs of observation. $**p < 0.01$ and $***p < 0.001$, Significantly different when compared with reference compound, Albendazole prototypes used for the study were designated as $D_3$, $D_4$, $D_7$, $D_8$ & $E_3$, $E_4$, $E_7$ and $E_8$ at 10mg/mL, 50mg/mL and 100mg/mL respectively and the standard drug Albendazole (ALB) was used at 10mg/ml.

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