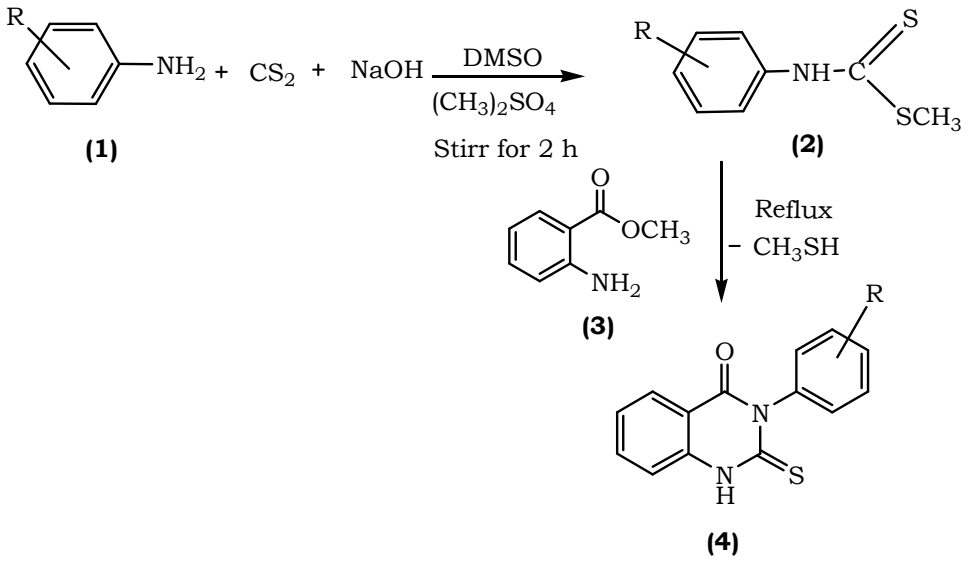
# 5. RESULTS AND DISCUSSION

## 5.1. Chemistry

### 5.1.1. Synthesis of 3-(substituted phenyl)-2-thioxo quinazolin-4(3*H*)-ones (4)

The key intermediate 3-(substituted phenyl)-2-thioxo quinazolin-4(3*H*)-ones (**4**) were synthesized by the straight forward method. In this synthetic scheme, substituted aniline **(1)** treated with carbon disulphide and sodium hydroxide in dimethyl sulphoxide to give sodium dithio carbomate, which was methylated with dimethyl sulphate to afford the dithio carbamic acid methyl ester (**2**), which upon reflux with methyl anthranilate (**3**) in ethanol yield the desired 3-(substituted phenyl)-2-thioxo quinazolin-4(3*H*)-ones **(4)** via the thiourea intermediate in good yield around 75%. The use of DMSO as the reaction solvent enhanced the rate of reaction and the use of alkali in higher concentration prevent the hydrolysis of the intermediate, probably due to less salvation. The product obtained was cyclic and not an open chain thiourea (**4**).

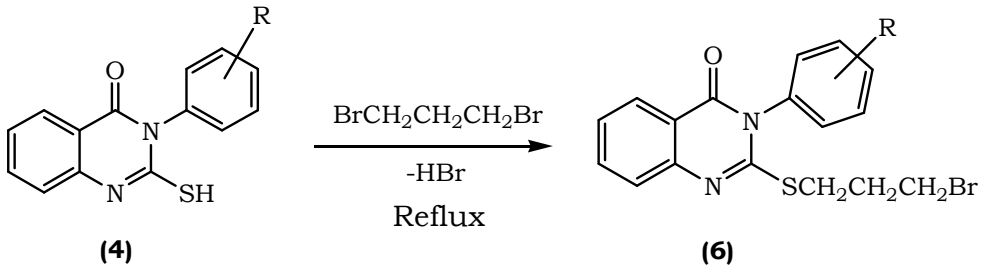



The IR spectrum of **4** show intense peaks around 3310-3220 $cm^{-1}$ for cyclic thiourea (NH), around 1680 $cm^{-1}$ for carbonyl (C=O) and around 1210 $cm^{-1}$ for thioxo (C=S) stretching. $^1H$ NMR spectrum of **4** showed multiplet around δ 7.00-8.20 ppm for aromatic proton and a singlet around δ 10.00 ppm indicating the presence of NH. Data from the elemental analyses have been found to be in conformity with the assigned structure. Further the molecular ion recorded in the mass spectrum is also in agreement with the molecular weight of the compound.

### 5.1.2 Synthesis of 2-(3-bromopropylthio)-3-(substituted phenyl) quinazolin-4(3*H*)-ones (6)

The 2-(3-bromopropylthio)-3-(substituted phenyl) quinazolin-4(3*H*)-ones **(6)** was prepared by heating a solution of

3-(substitutedphenyl)-2-thioxo-quinazolin-4(3*H*)-one **(4)**, and 1,3-dibromopropane in acetone in the presence of $K_2CO_3$ at reflux temperature.



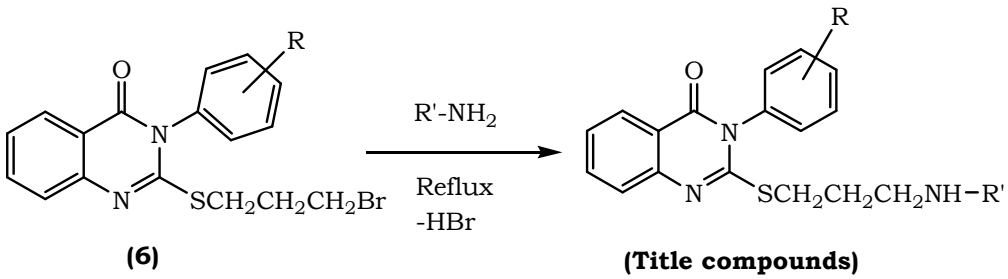

**(4)** **(6)**

The IR spectrum of **6** showed disappearance of NH and C=S stretching signals of cyclic thiourea. It showed a peak for carbonyl (C=O) stretching around 1167-1716 $cm^{-1}$. The $^1H$ NMR spectrum of compound **6** showed multiplet around δ 2.03-3.30 for $-SCH_2CH_2CH_3$ group and a multiplet for aromatic protons observed around at δ 7.21-8.27 Data from the elemental analyses and molecular ion recorded in the mass spectrum further confirmed the assigned structure. The M+2 peak observed in the product due to Br group further confirms the product.

### 5.1.3 Synthesis of 2-(3-substitutedpropylthio)-3-(substituted phenyl) quinazolin-4-(3*H*)-ones

The title compounds were obtained in fair to good yields through the nucleophilic displacement of –Br group of 2-(3-bromopropylthio)-3-(substituted phenyl) quinazolin-4-(3*H*)-one

(**6**) with a variety of amines, using ethanol as solvent to afford 2-(3-substituted propylthio)-3-(substitutedphenyl) quinazolin-4(3*H*)-ones.




**(6)** **(Title compounds)**

The formation of title compounds is indicated by the disappearance of peak due to -Br of the starting material and the appearance of NH signal around at between 3220-3320 $cm^{-1}$ in the IR spectra of the title compounds. The $^{1}H$ NMR spectra of the title compounds showed peaks for propyl substituents at C-2 and a singlet around δ 8.04 ppm due to NH, a multiplet around δ 6.89-8.31 ppm was observed for aromatic protons. In mass spectra of the title compounds the common peak appeared due quinazolin-4-one moiety cation at m/z 168. Elemental (C, H and N) analysis satisfactorily confirmed elemental composition and purity of the synthesized compounds.

## 5.2. Pharmacological investigation

### 5.2.1. i) Antihistaminic activity

Thirty compounds containing 2-(3-substituted propylthio)-3-(phenyl/substituted phenyl) quinazolines have been evaluated for their *in vivo* antihistaminic activity. Protection against histamine induced bronchospasm on conscious guinea pigs method was adopted to determine the antihistaminic potential of the test compounds. All of them have been found to exhibit good antihistaminic activity. Percentage protection data showed that all compounds of the series show significant protection in the range of 64-77%.

Structure activity relationship (SAR) studies indicated that different substituents on the N-3 aromatic ring, exerted varied biological activity. The electronic nature of the substituent group of N-3 aromatic ring led to a significant variation in antihistaminic activity. For example electron withdrawing group (chloro substituent) enhanced the biological activity, whereas electron releasing groups (methyl) made the compounds less active. SAR studies also indicated that different substituents over the C-2 position of quinazoline ring exerted varied biological activity. It has been found that the presence of diethyl group showed significant activity, when the cyclic amines with the similar lipophilicity are substituted (pyrrolidinyl compound and

piperidinyl Compound) the activity is retained. Placement of additional heteroatoms like nitrogen (piperazinyl compound and *N*-methyl piperazinyl compound) and oxygen (morpholinyl compound) leads to increase in activity. Placement of aryl substitutions (phenyl group; *p*-chlorophenyl group; *p*-methyl phenyl group) results in decreased activity. Placement of arylalkyl (benzyl compound) further decreased the activity. Among the series, 2-(3-(4-methyl piperazin-1-yl)propylthio)-3-(4-chloro phenyl) quinazolin-4(3*H*)-one **(PC-5)** exhibited the most potent activity with the percentage protection of 77.53 which is more potent than that of standard chlorpheniramine maleate (percentage protection 70.09%).

### 5.2.2. ii) Sedative-hypnotic activity

As sedation is one of the major side effects associated with antihistamines, the test compounds were also evaluated for their sedative potentials. Sedative-hypnotic activity was determined by measuring the reduction in locomotor activity using actophotometer on Albino Swiss mice. The results of sedative-hypnotic activity indicate that all the test compounds were found to exhibit only negligible sedation (6-12%), whereas the reference standard chlorpheniramine maleate showed 33% sedation.

**Table 1: Antihistaminic and sedative-hypnotic activity of compounds OT1-OT10**

| Compound Code | Time of onset of convulsion ( in Sec) | % Protection | Percent CNS Depression | | | |
|---|---|---|---|---|---|---|
| | | | 0.5 h | 1 h | 2 h | 3 h |
| **OT1** | 355+1.85* | 66.83+0.17* | 13.77±1.06** | 13.70±1.05** | 14.95±0.99** | 11.40±0.76** |
| **OT2** | 370+3.06* | 67.61+0.37* | 10.53±1.06** | 11.03±0.92** | 11.96±1.04** | 8.14±0.80** |
| **OT3** | 362+2.24* | 67.42+0.20* | 11.68±1.56** | 12.96±1.30** | 13.29±0.77** | 9.26±0.78** |
| **OT4** | 396+1.53* | 70.21+0.11* | 8.62±0.68** | 8.79±0.64** | 9.21±0.68** | 6.31±0.67** |
| **OT5** | 417+2.50* | 71.70+0.17* | 8.19±0.73** | 9.48±0.88** | 9.25±0.73** | 7.51±0.71** |
| **OT6** | 390+2.27* | 69.75+0.17* | 7.56±0.82** | 9.20±1.06** | 9.96±0.80** | 7.44±0.83** |
| **OT7** | 351+2.28* | 66.39+0.21* | 8.97±1.00* | 8.79±0.99** | 10.34±0.84** | 6.12±0.75** |
| **OT8** | 352+2.41* | 66.54+0.22* | 8.33±0.61** | 9.20±0.65** | 9.49±0.55** | 6.13±0.97** |
| **OT9** | 335+2.90* | 64.78+0.30* | 8.78±1.22** | 10.30±0.81** | 11.54±0.73** | 8.92±1.14** |
| **OT10** | 346+1.64* | 65.90+0.16* | 9.23±1.35** | 9.37±1.35** | 12.39±0.84** | 7.56±0.69** |
| Chlorpheniramine | 394+4.43* | 70.09+0.33* | 32.04+0.50** | 38.80+1.32** | 34.80+0.72** | 29.58+0.72** |
| Cetirizine | 551+16.89* | 78.95+0.32* | 4.5+0.53* | 9.6+0.93* | 11.6+0.83* | 8.3+0.65* |

Each value represents the mean ± SEM (n=6). Significance levels *p<0.001, **p<0.05.

**Table 2. Antihistaminic and sedative-hypnotic activity of compounds PC1-PC10**

| Compound Code | Time of onset of convulsion ( in Sec) | % Protection | Percent CNS Depression | | | |
|---|---|---|---|---|---|---|
| | | | 0.5 h | 1 h | 2 h | 3 h |
| **PC1** | 435+1.90* | 72.88+0.12* | 11.89±0.95** | 13.21±1.19** | 12.95±1.12** | 9.51±1.03** |
| **PC2** | 450+2.45* | 73.82+0.14* | 8.42±1.00** | 8.55±0.94** | 9.52±1.24** | 5.16±0.98** |
| **PC3** | 444+2.24* | 73.46+0.13* | 9.56±0.86** | 9.49±0.98** | 10.06±0.96** | 7.48±1.60** |
| **PC4** | 501+1.56* | 76.46+0.07* | 6.30±1.25** | 8.03±1.71** | 8.27±1.68** | 5.77±1.43** |
| **PC5** | 525+2.30* | 77.53+0.09* | 6.49±1.52** | 7.19±1.41** | 7.32±1.34** | 6.16±1.57** |
| **PC6** | 481+1.50* | 75.46+0.07* | 6.61±1.90** | 6.48±1.97** | 7.68±1.48** | 5.35±1.44** |
| **PC7** | 404+2.28* | 70.84+0.16* | 6.83±1.66** | 8.32±1.36** | 8.73±1.27** | 5.34±0.89** |
| **PC8** | 417+3.45* | 71.73+0.23* | 5.89±1.38** | 5.71±1.34** | 7.74±0.78** | 5.89±1.38** |
| **PC9** | 385+2.18* | 69.35+0.17* | 7.03±1.42** | 9.45±1.78** | 9.66±1.69** | 6.48±1.50** |
| **PC10** | 398+4.05* | 70.34+0.29* | 7.83±1.29** | 8.63±1.36** | 10.68±1.08** | 6.93±1.08** |
| Chlorpheniramine | 394+4.43* | 70.09+0.33* | 32.04+0.50** | 38.80+1.32** | 34.80+0.72** | 29.58+0.72** |
| Cetirizine | 551+16.89* | 78.95+0.32* | 4.5+0.53* | 9.6+0.93* | 11.6+0.83* | 8.3+0.65* |

Each value represents the mean ± SEM (n=6). Significance levels *p<0.001, **p>0.05.

**Table 3: Antihistaminic and sedative-hypnotic activity of compounds Ph1-Ph10**

| Compound Code | Time of onset of convulsion ( in Sec) | % Protection | Percent CNS Depression | | | |
|---|---|---|---|---|---|---|
| | | | 0.5 h | 1 h | 2 h | 3 h |
| **Ph1** | 379+1.85* | 68.88+0.15* | 12.00±1.20** | 13.02±1.22** | 13.60±1.26** | 9.81±1.52** |
| **Ph2** | 388+2.46* | 69.58+0.19* | 8.16±0.73** | 9.12±1.02** | 9.15±1.02** | 6.00±0.58** |
| **Ph3** | 381+1.82* | 69.02+0.14* | 10.13±0.55** | 10.14±0.56** | 11.16±0.77** | 8.03±0.91** |
| **Ph4** | 410+2.40* | 71.21+0.16* | 7.10±0.88** | 7.11±0.88** | 8.16±0.73** | 5.01±0.43** |
| **Ph5** | 441+2.43* | 73.23+0.14* | 7.10±0.88** | 8.16±0.73** | 8.19±0.76** | 6.00±0.58** |
| **Ph6** | 408+2.86* | 71.09+0.19* | 6.07±0.59** | 7.11±0.88** | 7.17±0.87** | 5.01±0.43** |
| **Ph7** | 365+1.52* | 67.66+0.13* | 7.10±0.88** | 7.11±0.88** | 9.81±1.52** | 6.00±0.58** |
| **Ph8** | 370+4.29* | 68.08+0.36* | 6.07±0.59** | 6.00±0.58** | 7.17±0.87** | 5.18±0.47** |
| **Ph9** | 356+4.56* | 66.82+0.42* | 8.16±0.73** | 8.18±0.74** | 10.13±0.55** | 6.07±0.59** |
| **Ph10** | 351+2.46* | 66.37+0.23* | 9.81±1.52** | 9.61±1.42** | 10.14±0.56** | 7.11±0.88** |
| Chlorpheniramine | 394+4.43* | 70.09+0.33* | 32.04+0.50** | 38.80+1.32** | 34.80+0.72** | 29.58+0.72** |
| Cetirizine | 551+16.89* | 78.95+0.32* | 4.5+0.53* | 9.6+0.93* | 11.6+0.83* | 8.3+0.65* |

Each value represents the mean ± SEM (n=6). Significance levels *p<0.001, **p>0.05

**Figure 6: Antihistaminic activity of compounds OT1-OT10**

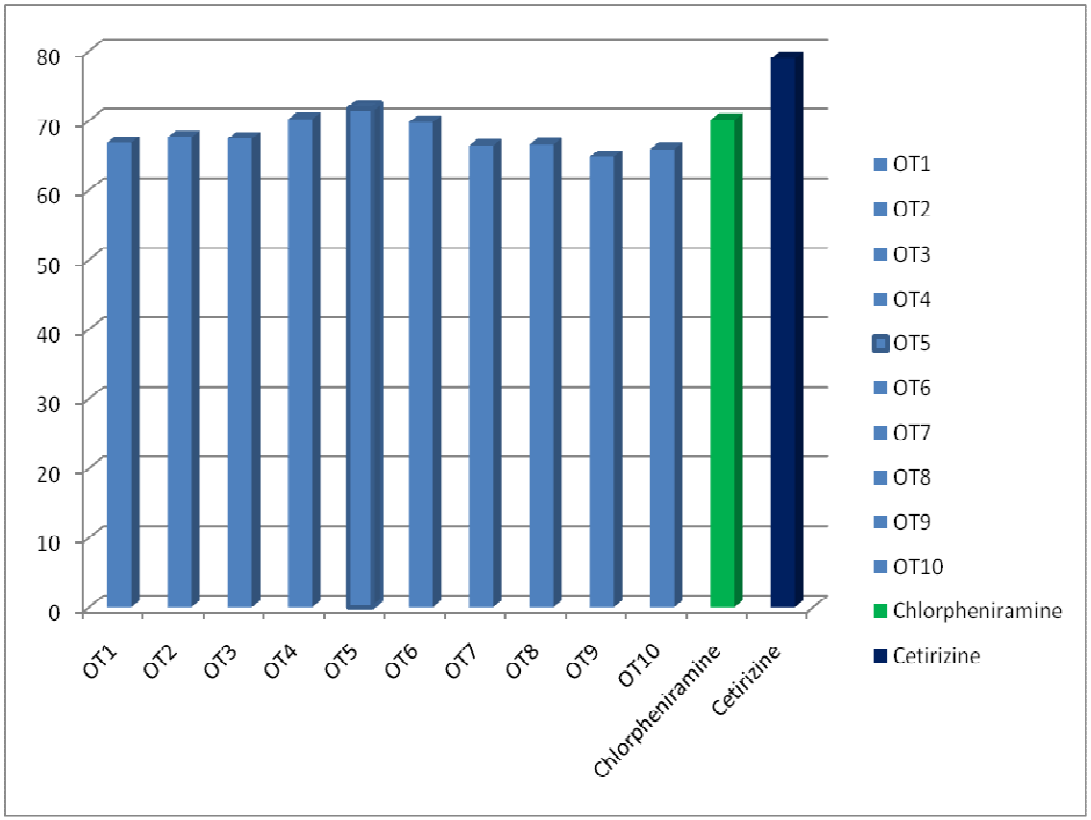


**Figure 7: Antihistaminic activity of compounds PC1-PC10**

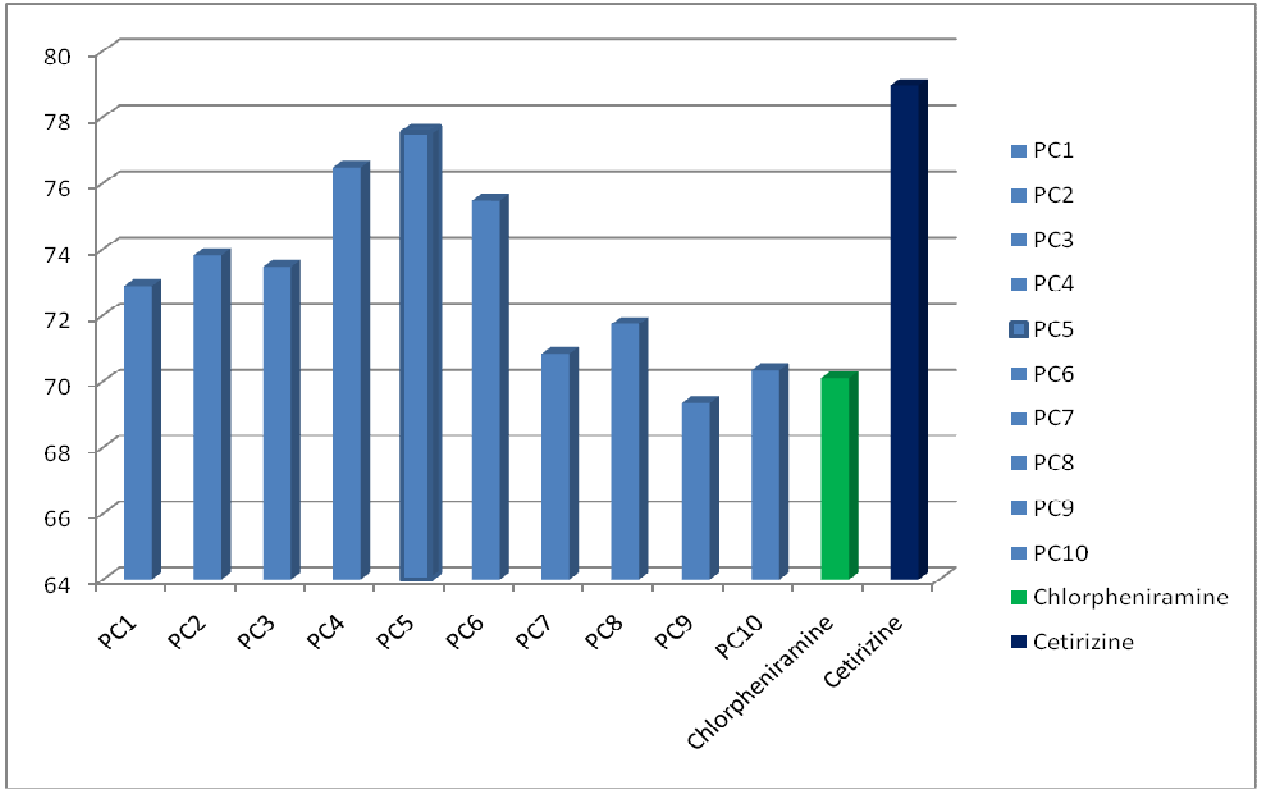


**Figure 8: Antihistaminic activity of compounds Ph1-Ph10**

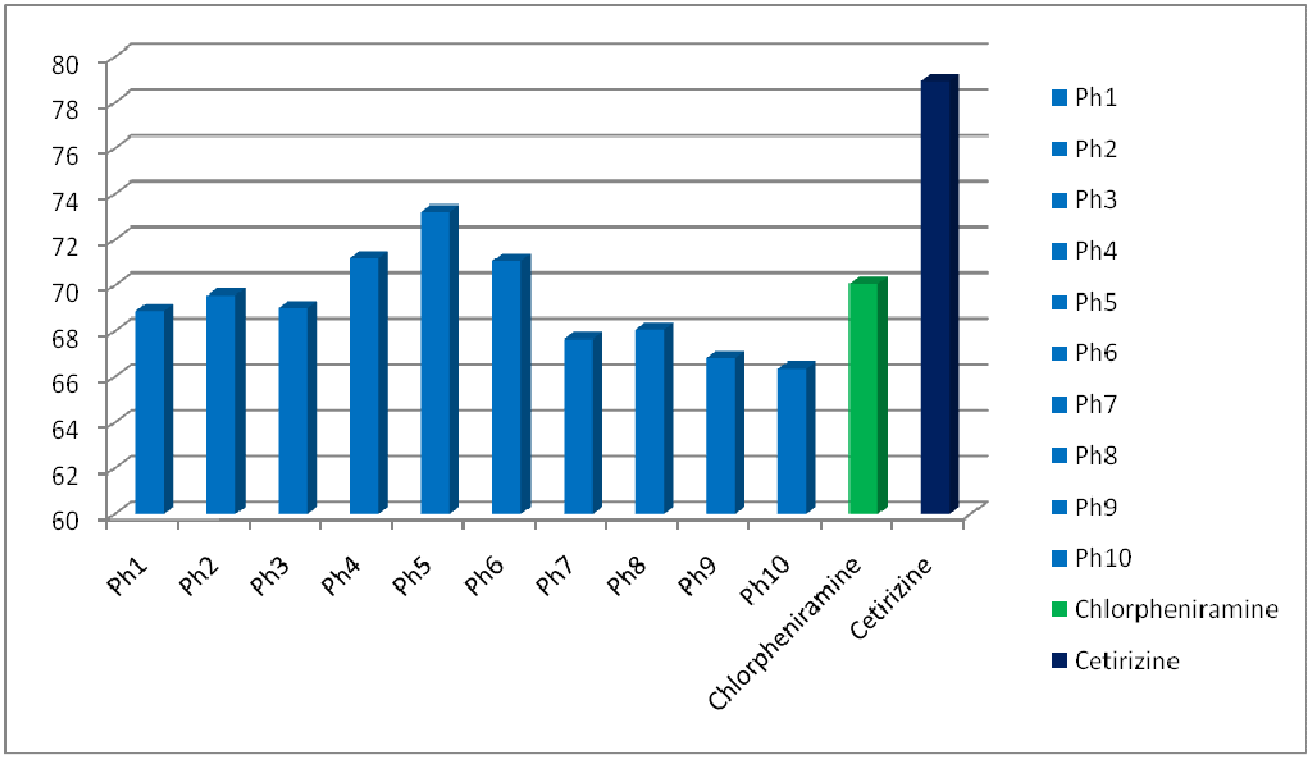


**Figure 9: Comparison of antihistaminic activity of series I** (OT1-OT10)**, series II** (PC1-PC10) **and series III** (Ph1-Ph10)

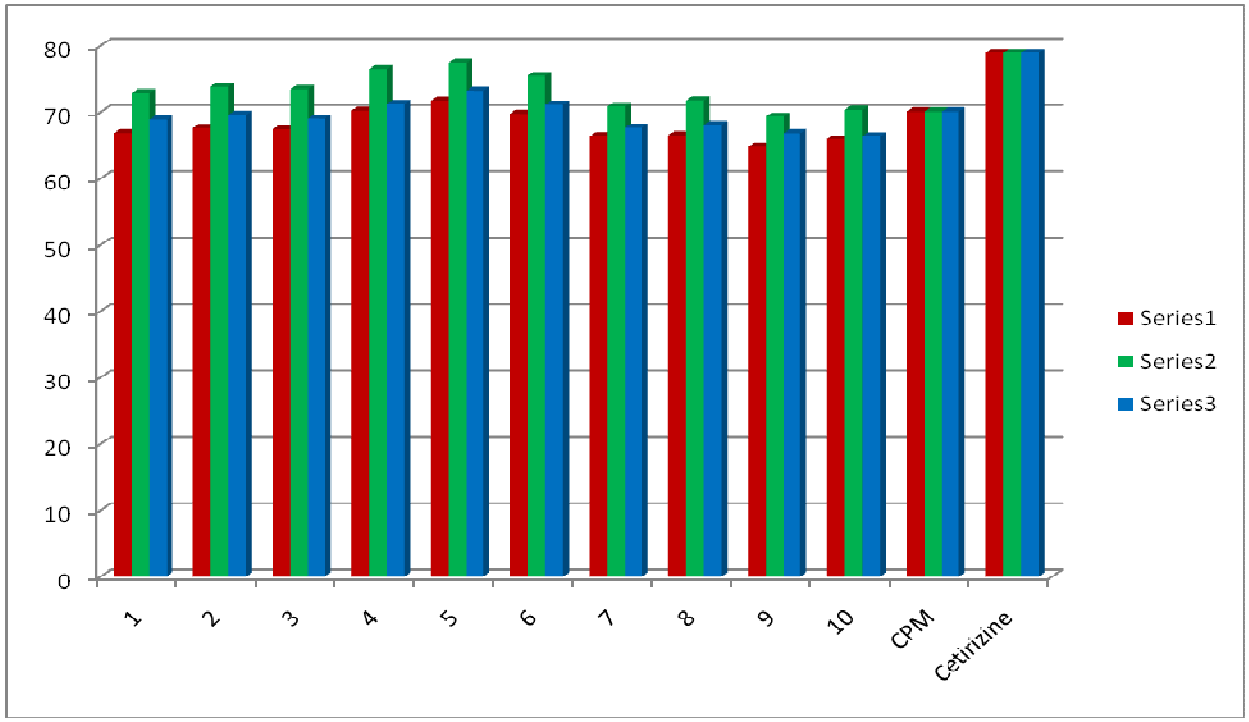


**Figure 10: Sedative-hypnotic activity of compounds OT1-OT10**

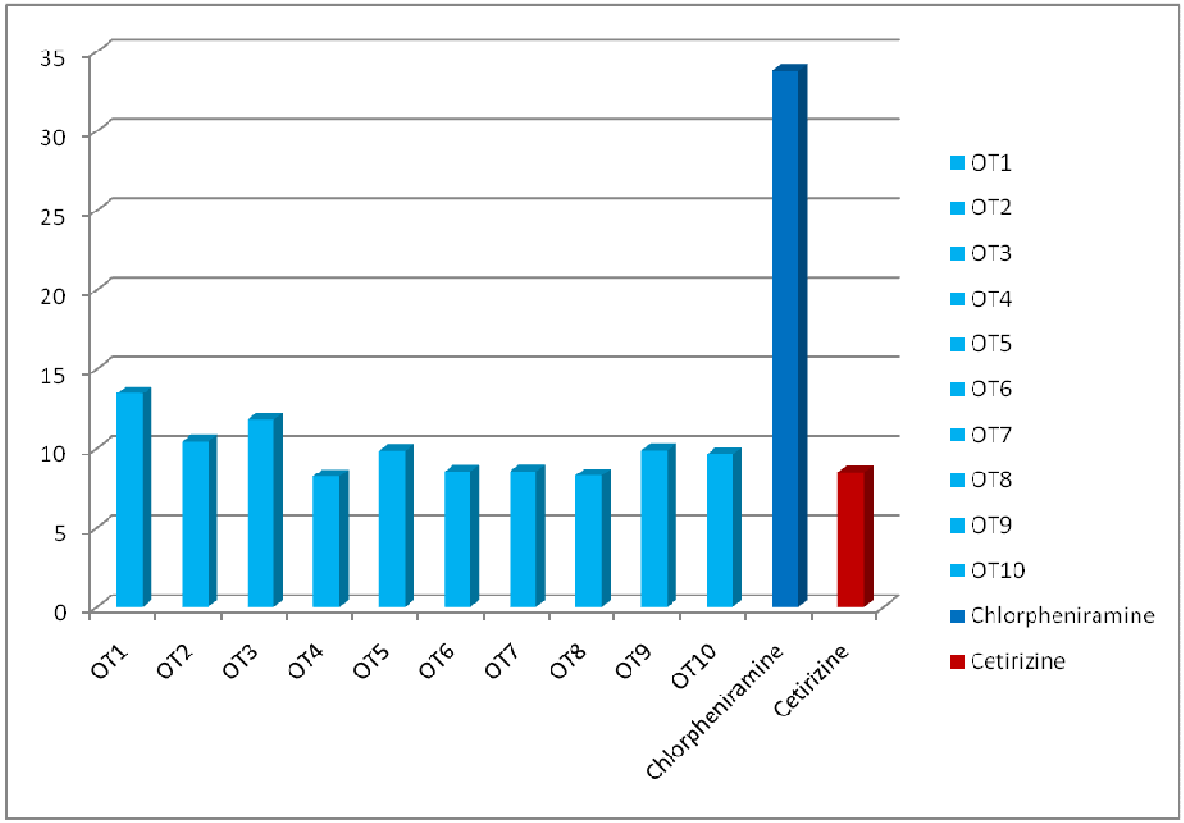


**Figure 11: Sedative-hypnotic activity of compounds PC1-PC10**

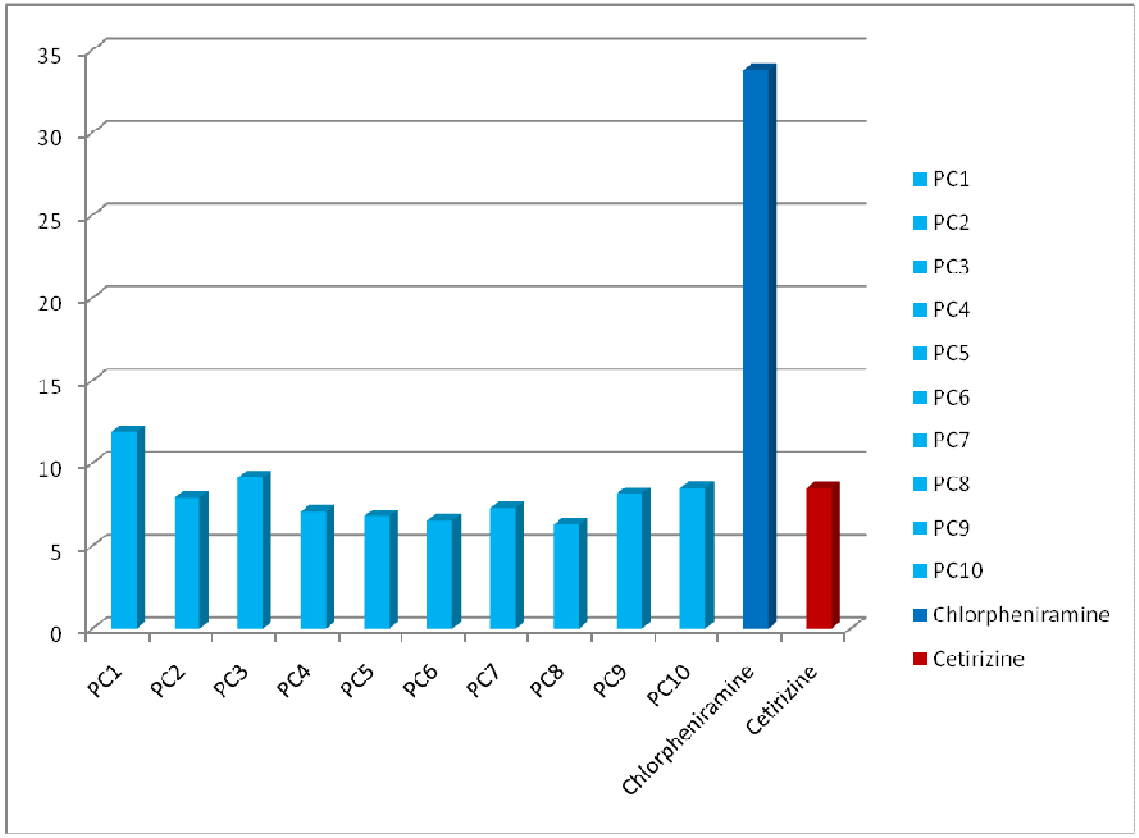


**Figure 12: Sedative-hypnotic activity of compounds Ph1-Ph10**

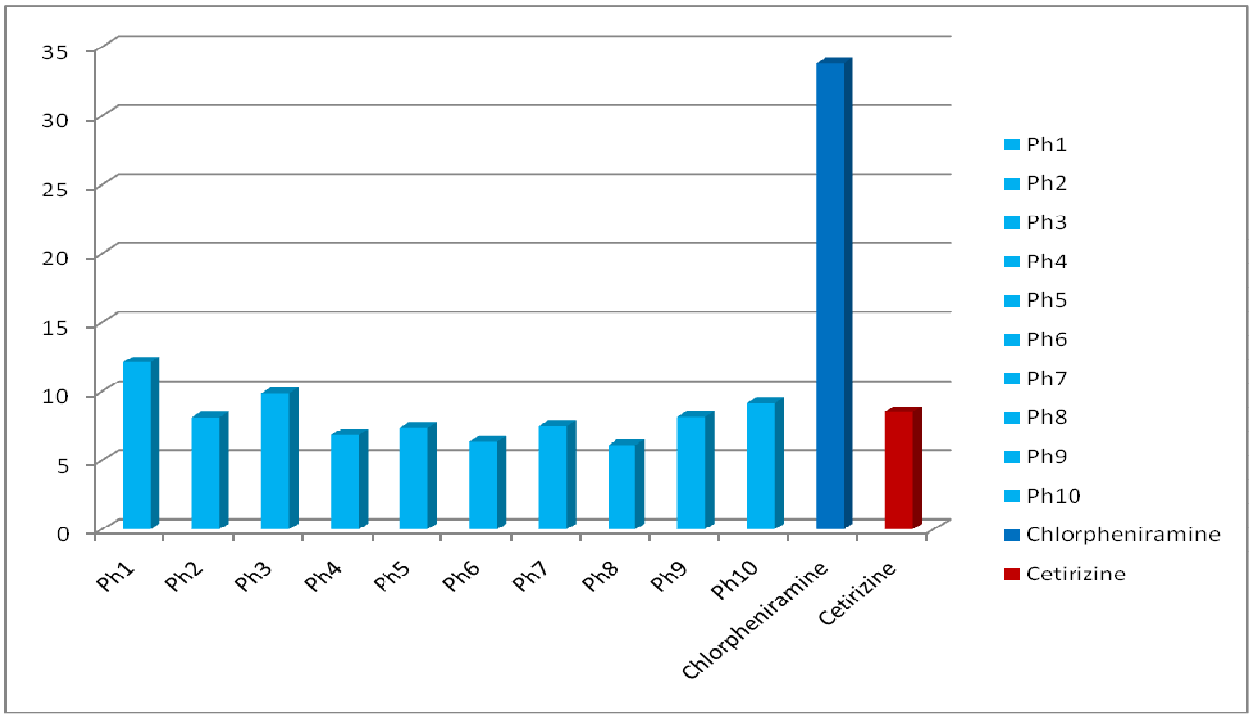


**Figure 13: Comparison of sedative and hypnotic activity of series I** (OT1-OT10)**, series II** (PC1-PC10) **and series III** (Ph1-Ph10)