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Synthesis and Antithyroidal Evaluation of N-Aryl Formamidino-N-(Substituted) Aryl Thiocarbamides

Swati Pawar*

ABSTRACT

Several N-aryl formamidino derivatives of thiocarbamides were synthesized. The structure and purity of the prepared compounds were characterized by elemental, spectral (IR) and TLC analysis. These molecules were evaluated for their efficacy as antithyroidals by radioactive iodine uptake method & the activity (Potency) of synthesized compounds were compared with standard drug Thiouracil.

Keywords: Thiocarbamides; Antithyroidal Activity; Toxicity.

1.0 Introduction

It is well known fact that some suitable, curative and corrective agents still remain to be developed for common diseases like thyroid diseases etc. The awareness of such critical problems and needs, directed intensive efforts to develop some useful antithyroid compounds which are more active and least toxic. A search for more active and least toxic substances led to the use of various thiocarbamide derivatives. The first observation leading to the development of organic antithyroid compounds such as thiocarbamides and thiouracils were published in 1941 and 1942. The action of thiocarbamide in relieving the symptoms of thyrotoxicosis appeared to be due to its ability to combine with iodine to form bis-formamidine hydrochloride and thus prevent the synthesis of d-iodothyronine and thyroxine.

2.0 Chemistry

The general sequence of the reaction may be depicted as follows:

3.0 Experimental

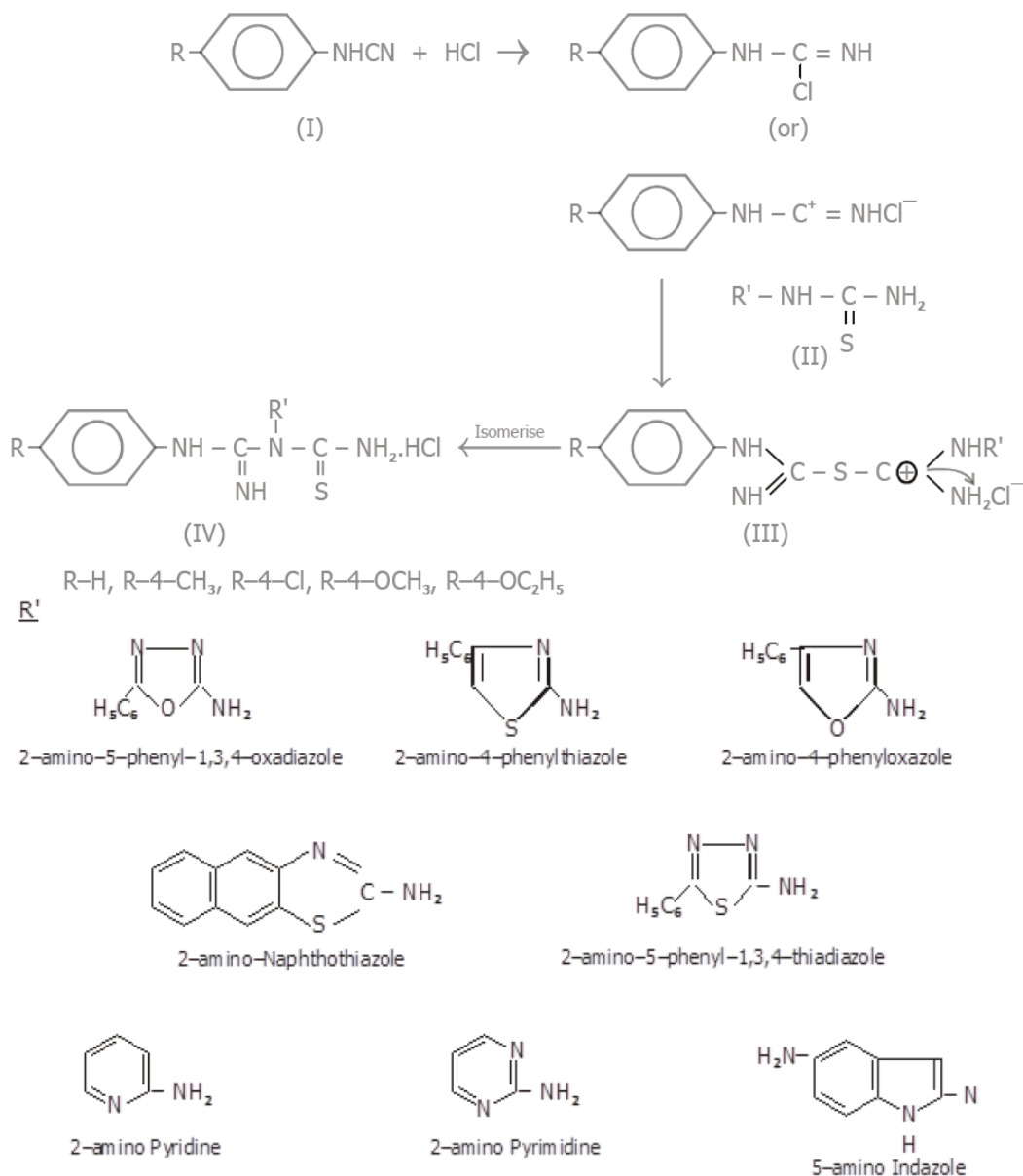
The melting points of the compounds were determined in open glass capillaries with the help of thermionic melting point apparatus and are

uncorrected. The homogeneity of all the newly synthesized compounds was routinely checked by TLC on silica gel G plates and spots were located by using iodine chamber. Elemental analysis of all the synthesized compounds were determined by a Perkin-Elmer 2400 elemental analyzer and results were found within the $\pm 0.4\%$ of theoretical values. IR spectra were recorded in KBr on a Perkin Elmer spectrum Rx-I, spectrometer.

4.0 Synthesis of N - Aryl Formamidino - N - 2 - [5-(4-Chlorophenyl) - 1, 3, 4 - Oxadiazolyl] Thiocarbamide Hydrochloride: (1) a, (1) b

Equimolecular quantities of phenyl cyanamide (2.36 gm, 0.02M) (which is prepared by a mixture of phenyl thiocarbamide dissolved in sodium hydroxide and freshly prepared lead hydroxide were heated on a water bath for 4 hours) in dry ether and N-2[-5-(4-chloro phenyl)-1,3,4-Oxadiazolyl] thiocarbamide (4.40 gm; 0.02M) (firstly 2-amino 5(4-chloro Phenyl)-1,3,4-oxadiazole was prepared by the oxidative cyclization of p-chloro benzaldehyde semicarbazone. Then Equimolecular quantities of benzoyl isothiocyanate (1.63; 0.01 M) and 2-amino -5-(4-chloro phenyl)-1, 3, 4-oxadiazole (1.61; 0.01M) in benzene (20 ml) was refluxed on water bath for 4-5 hours with constant stirring. The Crude product of N-2- [5(-4-chloro phenyl)-1, 3, 4 oxadiazolyl] -N- Benzoyl]

*Department of Applied Science, BIT, National Capital Region, Ghaziabad, Uttar Pradesh, India
(E-mail: Pawar.swati05@gmail.com)



thiocarbamide thus obtained was treated with petroleum ether (40–60°C) and then with solvent ether. The crystalline thiocarbamide so obtained was recrystallised. Now by the hydrolysis of this, N-2-[5-(4-chloro phenyl)-1, 3, 4-oxadiazolyl] thiocarbamide was obtained) in dry acetone were mixed and dry HCl gas was passed through the mixture for few minutes.

A white crystalline product was separated out in good yield. It could not be crystallized as it decomposed on boiling with any solvent. So it was purified by repeated washings of ether and acetone to remove unreacted reactants if any.

The product could be desulphided with alkaline plumbite solution. Yield: 52% m.p.; 190°C. Similarly, other N-aryl-formamidino-N-2[5-(4-chloro phenyl)-1, 3, 4-oxadiazolyl] thiocarbamide hydrochloride were synthesized and summarized in table I and II.

This hydrochloride was characterized by elemental analysis and presence of characteristic bands N=C=S (1515 cm⁻¹); C=N (1630 cm⁻¹); C=C (1535 cm⁻¹); and substituted benzene ring (775 cm⁻¹) in the IR spectra of these compounds. Anal. Calcd : for C₁₆H₁₄N₆Cl₂SO. Calculated: N: 20.54, S: 7.82; found: N: 20.53, S: 7.80.

5.0 Synthesis of N-Phenyl Formamidino-N-2-[5-(4-Methoxy Phenyl)-1,3,4-Thiadiazolyl] Thiocarbamide Hydrochloride - (2)

Bromine (0.1M) in glacial acetic acid (15 ml) was added slowly to stirred slurry of 4-methoxy benzaldehyde thiosemi-carbazone (0.1M) and powdered anhydrous sodium acetate (40 gm) in glacial acetic acid (130 ml.). Solid dissolved giving red solution.

After 15 minutes, it was poured into cold water and precipitated solid was washed and recrystallized from ethanol. The crystals of 2-amino-5-(4-methoxy phenyl)-1, 3, 4-thiadiazole thus formed by the condensation with benzoyl isothiocyanate gives the crystals of N-2-[5-(4-methoxy phenyl)-1, 3, 4-Thiadiazolyl]-N-benzoyl thiocarbamide. Now by the hydrolysis of this, N-2-[5-(4-methoxy phenyl)-1, 3, 4-thiadiazolyl] thiocarbamide was obtained. Condensation started with equimolecular quantities of phenyl cyanamide (0.01M) in dry ether and N-2-amino-[5-(4-methoxy phenyl)-1,3,4-thiadiazolyl] thiocarbamide (0.01M) in dry acetone were mixed and dry HCl gas passed through the mixture for few minutes.

A white crystalline product was separated out in good yield. It was purified by repeated washings of ether and acetone as it decomposed on boiling with any solvent.

The product could be desulphided with alkaline plumbite solution. Yield: 62% m.p. : 223°C. By adopting similar procedure various N-aryl formamidino- N-2-[5-(4-methoxy phenyl)-1,3,4-thiadiazolyl] thiocarbamide hydrochloride were synthesized and are tabulated in table III.

These hydrochlorides were characterized by elemental analysis: mol for C₁₇H₁₇CIN₆S₂O; Calc. N% 19.98, S% 15.22; found: N% 19.95, S% 15.20, and presence of characteristic bands in the I.R. Spectra. The I.R. Spectrum of these compounds showed characteristic bands N=C=S (1515 cm⁻¹), C=N (1630 cm⁻¹), C=C (1535 cm⁻¹) and substituted benzene ring (775 cm⁻¹).

6.0 Synthesis of N-phenyl Formamidino-N-2-[4-Chlorophenyl)-Oxazolyl] Thiocarbamide Hydrochloride - (3)

Equimolecular quantities of phenyl cyanamide (0.01M) in dry ether and N-2-amino- (4-chloro phenyl) oxazolyl thiocarbamide (0.01M) (which was synthesized from 2-amino-4-(p-chloro-phenyl) oxazole. In a clean conical flask p-chloro acetophenone (12 ml) is taken. To it bromine (5 ml) in dry benzene (4 ml) was added very slowly with constant stirring while keeping the flask in sunlight. The mixture was then shaken vigorously till the colour due to bromine was discharged urea (15 gms) was then added to the mixture and the flask was fitted with a double surface reflux condenser and the mixture was refluxed on a water bath for 27 hours. It was further heated for 3 hours after removing the condenser. The reaction product was then cooled, repeatedly extracted with ether, to remove the unreacted bromine and ketone to save it from becoming gummy.

The product was basified with ammonia and kept for 20 hours. It was then filtered and repeatedly washed with water, dried and finally crystallized from water: alcohol mixture. Thus obtained 2-amino-4-(p-chlorophenyl) oxazole condensation with Benzoyl isothiocyanate the compound N-2-[(4-chlorophenyl)-oxazolyl]-N-benzoyl thiocarbamide was prepared. By the hydrolysis of this N-2-(4-chlorophenyl)-oxazolyl] thiocarbamide was prepared) in dry acetone were mixed and dry HCl gas passed through the mixture for few minutes. A white crystalline product was separated out in good yield. It was purified by repeated washings of ether and acetone as it decomposed on boiling with any solvent.

The product could be desulphided with alkaline plumbite solution. Yield: 56%, M.P.: 161°C. Anal. found: N: 17.14%, S: 7.82%; calculated formula: C₁₇H₁₅N₅O₂Cl₂, N: 17.16%, S: 7.84%. By adopting similar procedure various N-aryl formamidino-N-2-[4-chlorophenyl oxazolyl] thiocarbamide hydrochlorides were synthesized and are tabulated in table IV.

These hydrochlorides were characterized by similar procedures of elemental analysis and presence of characteristic bands in the I.R. spectra. The I.R. spectrum of these compounds showed characteristic bands N=C=S (1515 cm^{-1}), C=N (1630 cm^{-1}); C=C (1585 cm^{-1}); and substituted benzene ring (775 cm^{-1}).

7.0 Synthesis of N-aryl Formamidino-(N-2-Naphthothiazolyl) Thiocarbamide Hydrochloride - (4)

Firstly 2-amino naphthothiazole was prepared by the oxidation of naphthyl thiourea with bromine in chloroform medium. Naphthyl thiourea (10 gms) was suspended in chloroform (50 ml) and solution of bromine (4 ml) in chloroform was added gradually with cooling and stirring of the reaction mixture. After allowing it to stand overnight, the chloroform was evaporated and the residue was treated with a little sodium bisulphite solution to remove the unreacted bromine.

The crude product was basified when a soft base is obtained which was then crystallized with aqueous alcohol. Now on the condensation of this naphthothiazole with Benzoyl isothiocyanate a compound N-2-naphthothiazolyl-N-benzoyl thiocarbamide was obtained. This was on hydrolysis changed into N-2-naphthothiazolyl thiocarbamide.

Now equimolecular quantities of N-2-naphthothiazolyl thiocarbamide (0.01M) in dry acetone and phenyl cyanamide (0.01M) in dry ether were mixed and dry HCl gas passed through the mixture for few minutes. A white crystalline product was separated out in good yield.

It was purified by repeated washings of ether and acetone as it desulphided with alkaline plumbite solution. yield: 86%, M.P. 160°C. By adopting similar procedure various N-aryl formamidino-N-2-naphthothiazolyl thiocarbamide hydrochlorides were synthesized and are tabulated in table V.

These hydrochlorides were characterized by elemental analysis and presence of characteristic bands in the I.R. spectra. The I.R. spectra of these compounds showed characteristic bands N=C=S (1515 cm^{-1}); C=N (1630 cm^{-1}); and substituted benzene ring (775 cm^{-1}). Molecular formula:

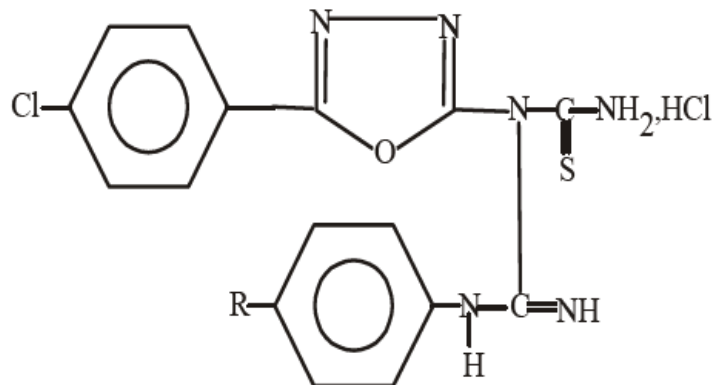
C₁₉H₁₆N₅ClS₂, Anal. Found: N% 16.90, S% 15.46; Calc.: N% 16.92, S% 15.47.

8.0 Synthesis of N-Aryl Formamidino-N-3-Pyridyl Thiocarbamide Hydrochloride and N-Aryl-Formamidino-N-4-Pyridyl Thiocarbamide Hydrochloride - (5a), (5b)

Equimolecular quantities of benzoyl isothiocyanate (0.01M) and 3-amino-pyridine (0.01M) in benzene (20 ml) was refluxed on water bath with constant stirring for 4-5 hours. The crude product of N-3-pyridyl-N-benzoyl thiocarbamide thus obtained was washed with petroleum ether (40-60) and then with solvent ether to remove unreacted isothiocyanate and 3-amino pyridine. It was then recrystallized with alcohol. The hydrolysis of N-3-pyridyl-N-benzoyl thiocarbamide was carried out and N-3-pyridyl thiocarbamide was obtained. Similarly condensation of 4-amino-pyridine with benzoyl isothiocyanate was carried out and preparation of 4-amino-pyridine and hydrolysis of N-4-pyridyl-N-benzoyl thiocarbamide was carried out. Equimolecular quantities of phenyl cyanamide (0.01M) in dry ether solution and 3-pyridyl thiocarbamide (0.01M) dissolved in dry acetone were mixed and dry HCl gas was passed through mixture for few minutes.

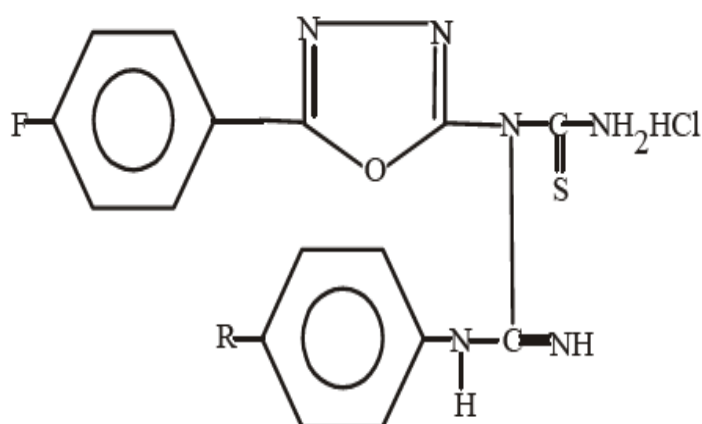
A white crystalline product was separated out in good yield which was filtered and washed freely with acetone and ether to remove unreacted constituents if any. It could not be recrystallized as it decomposed on boiling. Furthermore, it could be desulphided with alkaline plumbite solution. Yield: 70% MP 155-156°C. Using similar procedure as above other N-aryl-formamidino-N-3; N-aryl-formamidino-N-4-Pyridyl-thiocarbamide hydrochlorides have been synthesized and tabulated in table VI and VII. Characterizations of these compounds have been established on the basis of their analytical results and I.R. Spectra. An I.R. spectrum was obtained using KBr pallets and Perkin Elmer 720 infrared spectroscopy. I.R. Spectra show Characteristic bands in the region (1515 cm^{-1}), (1630 cm^{-1}), (1535 cm^{-1}) and (775 cm^{-1}) indicating the presence of N=C=S, C=N, C=C linkage and substituted benzene ring.

Table 1: Formation of *N*-Aryl formamidino-*N*-[5-(4-Chloro Phenyl)-1, 3, 4-Oxadiazol-2-yl] Thiocarbamide Hydrochloride



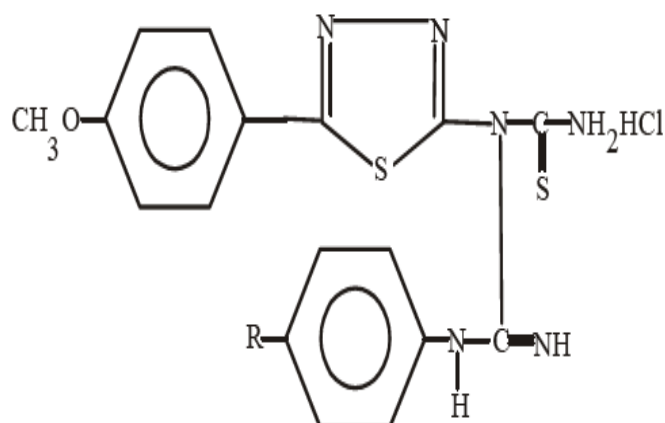
S. No.	R	Yield %	M. P. °C	Molecular formula	Elemental Analysis			
					N% Found	Calc.	S% Found	Calc.
1	H	52	190	C ₁₆ H ₁₄ N ₆ Cl ₂ SO	20.53	20.54	7.80	7.82
2	4-Cl	58	210	C ₁₆ H ₁₃ N ₆ Cl ₃ SO	18.92	18.94	7.20	7.22
3	4-CH ₃	62	202-03	C ₁₇ H ₁₆ N ₆ Cl ₂ SO	19.84	19.86	7.54	7.56
4	4-OCH ₃	65	221-22	C ₁₇ H ₁₆ N ₆ O ₂ Cl ₂ S	19.09	19.13	7.26	7.28
5	4-OC ₂ H ₅	68	181	C ₁₈ H ₁₈ N ₆ O ₂ Cl ₂ S	18.52	18.54	7.05	7.06

Table 2: Formation of *N*-Aryl Formamidino-*N*-[5-(4-Fluoro Phenyl) 1, 3, 4-Oxadiazol-2-yl] Thiocarbamide Hydrochloride



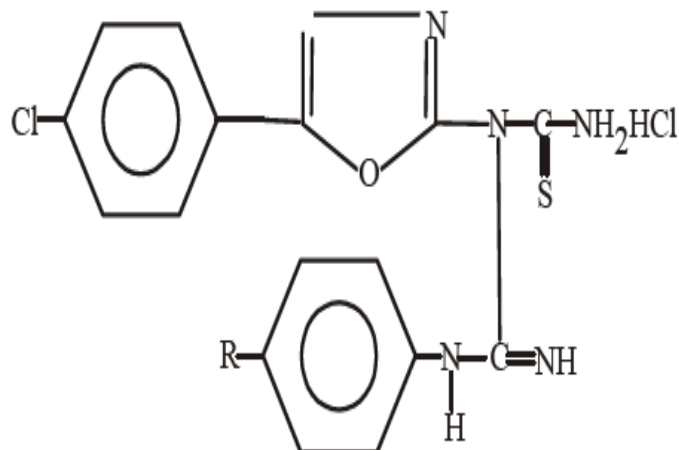
S. No.	R	Yield%	M.P.°C	Molecular formula	Elemental Analysis			
					N% Found	Calc.	S% Found	Calc.
1	H	64	176	C ₁₆ H ₁₄ N ₆ ClFSO	21.38	21.40	8.14	8.15
2	4-Cl	55	192	C ₁₆ H ₁₃ N ₆ Cl ₂ FSO	19.66	19.67	7.47	7.49
3	4-CH ₃	57	187	C ₁₇ H ₁₆ N ₆ ClFSO	20.65	20.66	7.86	7.87
4	4-OCH ₃	61	212	C ₁₇ H ₁₆ N ₆ O ₂ ClFS	19.86	19.88	7.54	7.57
5	4-OC ₂ H ₅	60	196	C ₁₈ H ₁₈ N ₆ O ₂ ClFS	19.21	19.24	7.31	7.33

Table 3: Formation of N-Aryl Formamidino-N-[5-(4-Methoxy Phenyl)-1, 3, 4-Thiadiazol-2-Yl] Thiocarbamide Hydrochloride



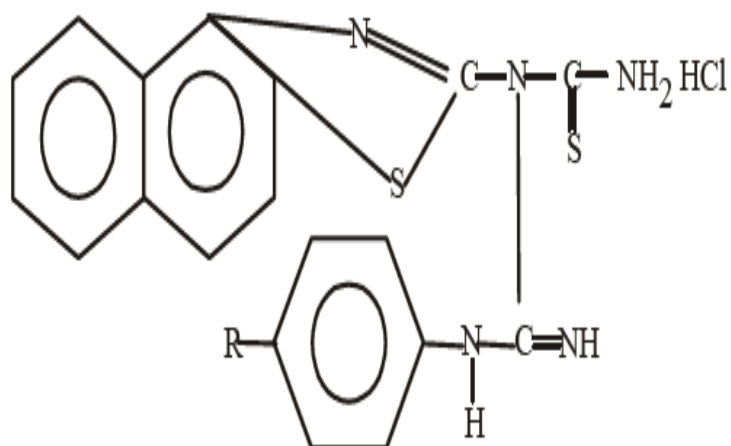
S. No.	R	Yield%	M.P.°C	Molecular formula	Elemental Analysis			
					N% Found	Calc.	S% Found	Calc.
1	H	62	223	C ₁₇ H ₁₇ ClN ₆ S ₂ O	19.95	19.98	15.20	15.22
2	4-Cl	65	215	C ₁₇ H ₁₆ Cl ₂ N ₆ S ₂ O	18.47	18.46	14.06	14.07
3	4-CH ₃	55	201	C ₁₈ H ₁₉ ClN ₆ S ₂ O	19.31	19.33	14.72	14.73
4	4-OCH ₃	52	219	C ₁₈ H ₁₉ ClN ₆ S ₂ O ₂	18.64	18.65	14.19	14.21
5	4-OC ₂ H ₅	57	187	C ₁₉ H ₂₁ ClN ₆ S ₂ O ₂	18.06	18.08	13.77	13.78

Table 4: Formation of *N*-Aryl Formamidino-*N*-(4-(5-Chloro Phenyl) Oxazol-2-Yl) Thiocarbamide Hydrochloride



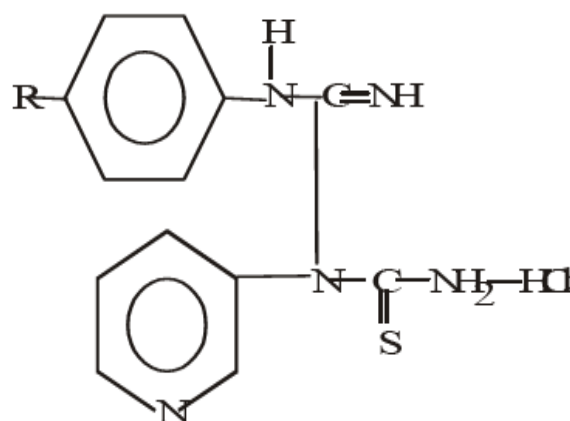
S. No.	R	Yield%	M.P.°C	Molecular formula	Elemental Analysis			
					N% Found	Calc.	S% Found	Calc.
1	H	56	161	C ₁₇ H ₁₅ N ₅ OSCl ₂	17.14	17.16	7.82	7.84
2	4-Cl	58	182	C ₁₇ H ₁₄ N ₅ OSCl ₃	15.80	15.82	7.21	7.23
3	4-CH ₃	62	176	C ₁₈ H ₁₇ N ₅ OSCl ₂	16.58	16.59	7.56	7.58
4	4-OCH ₃	68	193	C ₁₈ H ₁₇ N ₅ O ₂ SCl ₂	15.97	15.98	7.29	7.31
5	4-OC ₂ H ₅	65	170	C ₁₉ H ₁₉ N ₅ O ₂ SCl ₂	15.46	15.49	7.07	7.08

Table 5: Formation of *N*-Aryl Formamidino-(*N*-Naphthothiazol-2-Yl) Thiocarbamide Hydrochloride



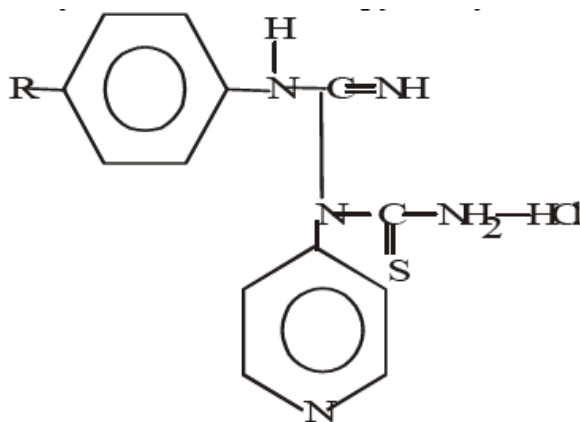
S. No.	R	Yield%	M.P.°C	Molecular formula	Elemental Analysis			
					N% Found	Calc.	S% Found	Calc.
1	H	66	160	C ₁₉ H ₁₆ N ₅ ClS ₂	16.90	16.92	15.46	15.47
2	3-Cl	60	191	C ₁₉ H ₁₅ N ₅ S ₂ Cl ₂	15.61	15.62	14.27	14.28
3	4-Br	70	185	C ₁₉ H ₁₅ N ₅ S ₂ ClBr	14.19	14.21	12.97	12.99
4	3-OCH ₃	55	172	C ₂₀ H ₁₈ N ₂ OS ₂ Cl	15.77	15.78	14.42	14.43
5	3-OC ₂ H ₅	50	202-03	C ₂₁ H ₂₀ N ₅ OS ₂ Cl	15.28	15.30	13.96	13.99

Table 6: Formation of N-Aryl Formamidino-(N-3-Pyrid-2-Yl) Thiocarbamide Hydrochloride



S. No.	R	Yield%	M.P.°C	Molecular formula	Elemental Analysis			
					N% Found	Calc.	S% Found	Calc.
1	H	70	155-156	C ₁₃ H ₁₄ N ₅ SCl	22.74	22.76	10.38	10.41
2	4-Cl	72	173	C ₁₃ H ₁₃ N ₅ SCl ₂	20.44	20.46	9.33	9.35
3	4-CH ₃	70	181	C ₁₄ H ₁₆ N ₅ SCl	21.75	21.77	9.94	9.95
4	4-OCH ₃	68	165	C ₁₄ H ₁₆ N ₅ SOCl	20.73	20.74	9.46	9.48
5	4-OC ₂ H ₅	65	182	C ₁₅ H ₁₈ N ₅ SOCl	19.90	19.91	9.07	9.10

Table 7: Formation of *N*-Aryl Formamidino-(*N*-4-Pyrid-2-Yl) Thiocarbamide Hydrochloride



S. No.	R	Yield%	M.P.°C	Molecular formula	Elemental Analysis			
					N% Found	Calc.	S% Found	Calc.
1	H	58	183	C ₁₃ H ₁₄ N ₅ SCl	22.75	22.76	10.38	10.41
2	4-Cl	56	164	C ₁₃ H ₁₃ N ₅ SCl ₂	20.45	20.46	9.33	9.35
3	4-CH ₃	61	192	C ₁₄ H ₁₆ N ₅ SCl	21.75	21.77	9.93	9.95
4	4-OCH ₃	55	172	C ₁₄ H ₁₆ N ₅ SOCl	20.72	20.74	9.47	9.48
5	4-OC ₂ H ₅	66	191	C ₁₅ H ₁₈ N ₅ SOCl	19.89	19.91	9.09	9.10

9.0 Pharmacological Screening

One of the best methods which is widely used now-a-days for determining the activity of chemical compounds is based upon the uptake of radioactive iodine by thyroid glands. The use of radioactive iodine has permitted investigators to follow a test dose of iodine from the time of its administration until its final excretion from body. Rawson and McGinty *et.al.* fed rats with various antithyroid compounds and then injected radioactive iodine, sacrificed the animal 3 hours later and measured the radio-iodine in thyroid glands. The percentage decrease in uptake value as compared with control glands gave activity for these compounds.

The method used for the evaluation of antithyroid activity of compounds was based on the work of Rawson and McGinty *et.al.* and was modified as follows:

Just weaned male albino rats (21–24 days old) weighing 30–45 gm were kept on low iodine diet

for 3 days and then divided into experimental groups consisting of 5 animals in each group. The animals in each group received an intraperitoneal injection of 0.2 ml of blank (0.9% NaCl), thiouracil or one of the test compounds. One hour later 1 Ci of NaI125 (carrier free) the animals were weighed and sacrificed. Their thyroid glands were removed and weighed. Thyroid glands were placed in 1 ml. of conc. HNO₃ as per procedure described by Perek and Bedrak and other for the thyroid of birds.

Counting of radioactivity was done in well type gamma scintillation counter. The background was subtracted and uptake (CpM) of radioactivity by the thyroid gland/ mg of the fresh tissue was calculated. The uptake by the control rate was considered as the base and considering this as 100% uptake, the percentage uptake of various standards taken and the unknown were calculated.

The following amount of thiouracil was taken to find out the correlation between the dose and response in the form of I125 uptake by the thyroid.

S1 0.25 mg

S2 0.50 mg

1 mg of each of the synthesized compounds was injected in an aqueous solution in 0.2 ml or more depending upon the solubility of compounds.

10.0 Result and Discussion

Various substituted derivatives of thiocarbamides were synthesized and screened for their antithyroidal activity. In compound (1a), replacement of aryl group with p-tolyl, p-anisyl caused the conversion of compound into antithyroid compound but the activity was much below than the compound, with the activity of thiouracil (table I).

In compound (1b), replacement of p-chlorophenyl and p-anisyl converted the compound to thyroid stimulatory compound rather than antithyroid compound (Table II).

In compound (2), the replacement of the aryl group by p-anisyl group caused the conversion of compound into antithyroid but the activity was much low as p-anisyl group caused a stimulatory effect on thyroid (table III).

In compound (3), p-phenityl group showed antithyroid activity but the activity was very low. Replacement of p-methyl group produced stimulatory effect on the thyroid (table IV).

In compound (4), the replacement of aryl group by O-methoxy group showed antithyroid activity which is much less than the activity of well known reported drug thiouracil (table V).

In compound (5a), the replacement of aryl group with p-chloro phenyl, p-phenityl, showed a stimulatory effect on the thyroid. (Table VI).

In compound (5b), the replacement of aryl group by p-tolyl and p-anisyl caused antithyroid activity which is not even 25% of the activity of the reported drug thiouracil (table VII).

11.0 Conclusion

On the basis of structure activity relationship, it is concluded–

1. The activity of (1a) compound was much below than the compound with the activity of thiouracil.
2. Compound (1 b) showed thyroid stimulatory effect rather than antithyroid compound.

3. The activity of compound (2) was much low as p-anisyl group caused a stimulatory effect on thyroid.
4. Compound (3), p-phenityl group showed antithyroid activity but the activity was very low. P-methyl group produced stimulatory effect on the thyroid.
5. Compound (4), aryl group replaced by O-methoxy group showed antithyroid activity which is much less than the activity of well known drug thiouracil.
6. Compound (5a), p-chloro phenyl, p-phenityl, showed a stimulatory effect on the thyroid.
7. Compound (5 b), p-tolyl and p-anisyl caused antithyroid activity which is not even 25% of the activity of reported drug thiouracil.

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