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Synthesis and biological activities of N-[(2´-Substituted phenyl)-1´, 3´-thiazol-5-one]-naphtho[2,1-b]furan-2-carboxamide derivatives

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ABSTRACT

Peptic ulcer is an ulcer of the mucous membrane lining those parts of the alimentary tract exposed to digestive juices or a necrotic lesion characterized by a crater like erosion of the stomach wall (gastric ulcer) or the duodenum (duodenal ulcer) often associated with painful symptoms. Thiazole derivatives have been reported to possess antiulcer activity. With the view to study antiulcer, antibacterial and antitubercular activities, we have synthesized some new thiazole derivatives and screened them for the same. A mixture of 2-hydroxy-1-naphthaldehyde, ethyl bromoacetate and anhydrous potassium carbonate in dry acetone was heated under reflux for 24.35 hours and then filtered which yielded Naphthyl [2,1-b]furan-2-ethyl carboxylate which was mixed with hydrazine hydrate in ethanol and refluxed for 18.3 hours to yield Naphtho [2,1-b]furan-2-carbohydrazide. A solution of various substituted aldehydes in ethanol was added to a solution of naphtho[2,1-b]furan-2-carbohydrazide in DMF, refluxed for 8.2 hours poured into crushed ice and then filtered to give N-[Substituted benzylidene]- naphtho [2,1-b]furan-2-carboxamide which were dissolved in 1,4-dioxan, mercaptoacetic acid and zinc chloride was refluxed for 14.4 hours to yield N-[Substituted phenyl]- 1',3'-thiazol-5-one]-naphtho [2,1-b]furan-2-carboxamide. It was observed that among ten compounds synthesized only three compounds showed potent antiulcer activity. Only four compounds showed significant antibacterial activity. These compounds were further subjected for Antitubercular activity and all the four showed sensitivity at concentrations 50 and 100 µg/ml.

Keywords: synthesis of N-[(2´-Substituted phenyl)-1´, 3´-thiazol-5-one]-naphtho[2,1-b]furan-2-carboxamide derivatives, Antiulcer activity, antitubercular activity.

INTRODUCTION

A peptic ulcer, also known as , PUD or peptic ulcer disease[1] is an ulcer (defined as mucosal erosions equal to or greater than 0.5 cm) of an area of the gastrointestinal tract that is usually

acidic and thus extremely painful. As many as 70-90% of ulcers are associated with *Helicobacter pylori*, a spiral-shaped bacterium that lives in the acidic environment of the stomach; however, only 40% of those cases go to a doctor. Ulcers can also be caused or worsened by drugs such as aspirin and other NSAIDs[2]. Ulcers can occur at any age, although they are rare in children and teenagers. Duodenal ulcers usually first occur between the ages of 30-50 years and are twice as common in men as well as in women. Stomach (or gastric) ulcers usually occur in people older than 60 years and are more common in women. Peptic ulcers are a very common condition in the United States and throughout the world. In the United States, an estimated 25 million people will suffer an ulcer at some point. That's 1 in 10 people. About 4 million people are affected by ulcers at any given time. There are approximately 350,000-500,000 new cases and more than 1 million ulcer-related hospitalizations each year in INDIA alone. About 6000 people die each year of ulcer-related complications[3].

A mixture of 2-hydroxy-1-naphthaldehyde, ethyl bromoacetate and anhydrous potassium carbonate in dry acetone was heated under reflux for 24.35 hours. The reaction mixture was filtered and potassium carbonate was washed with acetone which was evaporated to get carboxylate. To this hydrazine hydrate and ethanol was added and refluxed for 18.3 hours. The excess ethanol was distilled off to get the respective carbohydrazide. The obtained product was mixed with a solution of various substituted aromatic aldehydes in ethanol in DMF. The reaction mixture was refluxed for 8.2 hours, cooled to room temperature and poured into crushed ice to yield carboxamide. To carboxamide in 1,4 dioxan was added mercaptoacetic acid and catalytic amount of anhydrous zinc chloride. The mixture was refluxed for 14.4 hours, cooled and poured into sodium bicarbonate solution to remove unreacted mercaptoacetic acid which was filtered, to get the final products.

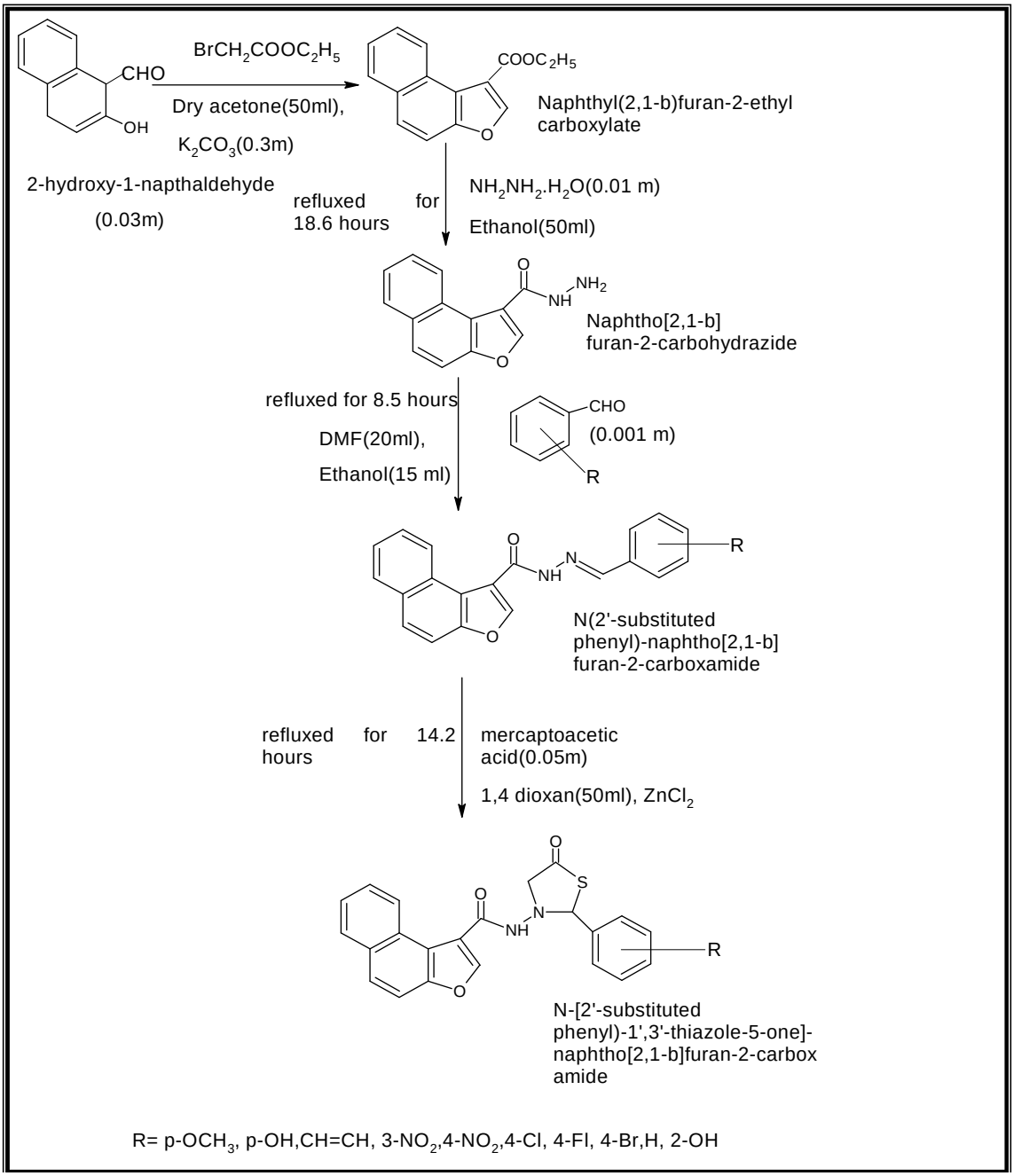
Table No. 1: Physicochemical properties of newly synthesized thiazole derivatives

Compounds Code	R	Molecular Weight	% Yield	M.P ^{0}C
A	0-OH	404	64	291-293
B	p-OH	404	72.87	294-296
C	p-Br	467	64.65	272-274
D	Phenyl	388	69.68	254-256
E	p-OCH_3	418	55.25	295-297
F	p-NO_2	433	53.4	293-296
G	m-NO_2	433	66	289-291
H	p-Cl	422	62.29	281-283
I	p-F	406	53.72	273-276
J	Vinyl	419	59.63	250-252

MATERIALS AND METHODS

All the melting points reported were determined in open capillaries using melting point apparatus expressed in $^{\circ}$C and are uncorrected. All the reactions were monitored by TLC using Methanol: Ethyl acetate (2:1) and Hexane: Ethyl acetate (3:2) and detected by using iodine as visualizing agent. The IR Spectra of the compounds were recorded on Shimadzu 1320 FT-IR spectrometer (KBr pellets method). Nuclear magnetic resonance spectra were obtained on DMM X-200 MHz Brookfield from Astra zeneca Ind. Ltd using cm^{-1} and chemical shift (δ) are reported in parts per million downfield from standard reference Tetramethylsilane (TMS). Mass spectra were

recorded on a LC-MS-2010 A using Auto spectro ionization-negative ion mode. All the solvents and reagents were purified and dried according to the procedures given in Vogel's Textbook of practical organic chemistry.



Synthesis of Naphthyl[2,1-b]furan-2-ethyl carboxylate[4]:

A mixture of 2-hydroxy-1-naphthaldehyde (0.03 m), ethyl bromoacetate (0.03 m) and anhydrous potassium carbonate (0.3 m) in dry acetone (50 ml) was heated under reflux for 24.35 hours. The reaction mixture was filtered and potassium carbonate was washed with acetone. Evaporation of

the solvent from the filtrate yielded the product which was recrystallized from ethanol to get reddish brown crystalline product. IR (KBr) cm^{-1}:2983 (C-H, str-aromatic), 1759 (C=O), 1666 (C=C) and 1257 (C-O-C). ^{1}H NMR (DMSO): δ1.3 (d, 3H,-CH_3), 4.3 (dd, 2H, -CH_2), 7.1-8.1 (m, 6H, Ar) and 8.9 (s, 1H, -CH- Furan ring). MS (m/z) : M^{+1} 241.

Synthesis of Naphtho[2,1-b]furan-2-carbohydrazide[5]:
A mixture of Naphthyl[2,1-b]furan-2-ethyl carboxylate (0.01 m), hydrazine hydrate (0.01 m) and ethanol (50 ml) was heated under reflux for 18.3 hours. The excess ethanol was distilled off and the solid which seperated out was collected by filtration, dried and rerystallized from ethanol. IR (KBr) cm^{-1} : 3327, 3257 (NH_2, NH-str), 2920 (C-H, str-aromatic), 1732 (C=O), 1678 (C=C) and 1242 (C-O-C). ^{1}H NMR (DMSO): δ 4.8 (s, 2H, NH_2). 7.4-8.1 (m, 6H, Ar), 8.8 (s, 1H, -CH- Furan ring), 9.3 (s, 1H, -NH). MS (m/z) : M^{+1} 228.

Synthesis of N-[Substituted phenyl]-Naphtho[2,1-b]furan-2-carboxamide[6]:
A solution of various substituted aldehydes (0.001 m) in ethanol (15 ml) was added to a solution of naphtho[2,1-b]furan-2-carbohydrazide (0.001 m) in DMF (20 ml). The reaction mixture was refluxed for 8.2 hours, cooled to room temperature and poured into crushed ice to yield the product. The crude product that seperated out was filtered and recrystallized from ethanol. IR (KBr) cm^{-1} : 3209 (NH-str), 2920 (C-H, str-aromatic), 2845 (-OCH_3), 1685 (C=O), 1602 (C-N), 1506 (C=C) and 1249 (C-O-C). ^{1}H NMR (DMSO): δ 7.28 (dd, 1H, -CH- Furan ring), 7.32 to 8.44 (m, 10H, Ar-H), 8.71 (s, 1H, CONH) and 11.71 (s, 1H, -N=CH-). MS (m/z) : M^{-2} 391.(R = H)

Synthesis of N-[(Substituted phenyl)-1',3'-thiazol-5-one]-Naphtho[2,1-b]furan-2-carboxamide[7]:
To N-[substituted phenyl]-naphtho[2,1-b]furan-2-carboxamide (0.05 m) in 1,4 dioxan (50 ml) was added mercaptoacetic acid (0.05 m) and catalytic amount of anhydrous zinc chloride. The mixture was refluxed for 14.4 hours, cooled and poured into sodium bicarbonate solution to remove unreacted mercaptoacetic acid. The residue was filtered, dried and recrystallized from ethanol. IR (KBr) cm^{-1} : 3232 (-NH str, -CONH), 2922 (C-H str, Ar), 1685 (C=O str, thiazole), 1581 (>C=O, CONH), 1228 (C-O-C), 810 (-Br). ^{1}H NMR (DMSO): δ 2.502 and 2.509 (s, 2H, -CH_2, thiazolidinone ring), 3.322 (s, 1H, N-CH-S, thiazolidinone ring), 5.647 (s, 1H, -CH- Furan ring), 7.458 (m, 10 H, Ar-H) and 8.708 (s, -CONH). MS (m/z) : M^{+1} 468. (R = H)

Antiulcer activity[8]:
Aspirin induced modified pylorus ligated model :
Adult Albino wistor rats(180-250g) were divided into 12 groups of six animals and fasted for 48 hrs.
Group 1: Served as solvent control.
Group 2: Received Ranitidine as Standard (27 mg/kg b.w.p.o.)
Group 3 to 12: Received newly synthesized compounds at a dose of 40 mg/kg b.w.p.o.

In aspirin-induced ulcerogenesis in pylorus ligated rats, aspirin was administered at a dose of 200 mg/kg orally in a suspension prepared in 0.3% CMC, 1h prior to pyloric ligation. The test drugs were administered twice daily for 2 days and standard drugs were administered orally once daily for 2 days prior to and one hour before Aspirin administration. Gastric juice was collected

centrifuged and subjected to various biochemical analysis like gastric volume, pH, free acidity, total acidity and total protein content. The mucosa was flushed with saline and the stomach pinned on a frog board. Then ulcer index and % inhibition was calculated.

Table No. 2: Effect of newly synthesized Naphtho[2,1-b]furan-thiazole derivatives on Aspirin plus pylorus ligation model and on the total protein content

Compound/ Standard	Dose (mg/kg body weight)	Ulcer Index	% Ulcer Protection	Total Protein(g/dl)
A	40	12.16±0.4773^{ns}	7.79±0.072	0.332±0.02426*
B	40	0.08±0.083***	99.77±0.080	0.282±0.008179***
C	40	0.5±0.1155***	96.145±0.011	0.187±0.01777***
D	40	9.48±0.2774^{ns}	26.92±0.0094	0.3149±0.003921*
E	40	9.65±0.329^{ns}	26.93±0.013	0.293±0.06361**
F	40	0.133±0.080***	99.93±0.031	0.2307±0.007194***
G	40	6.08±0.227^{ns}	53.84±0.016	0.4998±0.01963^{ns}
H	40	1.55±0.076**	88.45±0.010	0.4349±0.009033^{ns}
I	40	1.56±0.09**	88.46±0.0026	0.509±0.004122^{ns}
J	40	3.03±0.22*	76.92±0.0058	0.5073±0.005193^{ns}
Control	-	13.18±0.0609	-	0.601±0.0046
Standard (Ranitidine)	27	2.05±0.07638**	84.616±0.003	0.216±0.0095***

Values are expressed as Mean ± S.E.M (n=6). One Way ANOVA followed by Dunnet's test.
Where, *** represents extremely significant at $p < 0.001$ ** represents highly significant at $p < 0.01$, *represents significant at $p < 0.05$, ^{ns} represents non significant at $p > 0.05$.

Table No. 3: Antisecretory effects of newly synthesized Naphtho[2,1-b]furan-thiazole derivatives on Aspirin plus pylorus ligation model

Cpds	Dose (mg/kg body weight)	Gastric Volume (ml)	pH	Free Acidity (mEq/l/100g)	Total Acidity (mEq/l/100g)
A	40	2.137±0.1082^{ns}	6± 0.3651^{ns}	52.57± 0.5574^{ns}	72.17± 0.6009^{ns}
B	40	1.458±0.0094**	6.8±0.4282**	31.17± 0.8724**	40.83± 0.633**
C	40	0.342± 0.144**	7.2± 0.333**	20.33± 0.4216***	26.67± 0.9189***
D	40	2.712± 0.008$^{\#}$	5± 0.3651^{ns}	48± 0.8944^{ns}	63± 1.155^{ns}
E	40	4.198± 0.158**	6.5± 0.2236^{ns}	37.17± 1.249**	41.67± 4.356**
F	40	4.70± 0.0061**	7.0± 0.3651**	21.5± 0.4282***	25.5± 0.5774***
G	40	2.61± 0.280^{ns}	6.33±0.211^{ns}	44.67± 1.856^{ns}	49.3± 1.095^{ns}
H	40	0.9± 0.1238**	7.1± 0.2236**	21.17± 0.7293***	27.3± 0.8815***
I	40	1.99± 0.068**	6.67± 0.211^{ns}	64.5± 4.87^{ns}	75.67± 5.226^{ns}
J	40	2.502±0.1003**	6.33± 0.33^{ns}	52.67± 1.085^{ns}	69.5± 0.9574^{ns}
Control		2.662±0.11771	5.5± 0.2236	76.17± 4.370	93.67± 3.457
Standard (Ranitidine)	27	1.15± 0.1784**	7.3± 0.2236**	21.7± 1.893***	26.82± 1.893***

Values are expressed as Mean ± S.E.M (n=6). One Way ANOVA followed by Dunnet's test.
Where, *** represents extremely significant at $p < 0.001$ ** represents highly significant at $p < 0.01$, *represents significant at $p < 0.05$, ^{ns} represents non significant at $p > 0.05$.

Antimicrobial acitity[9]:

The synthesized compounds were tested for their antimicrobial activity by the disk diffusion method against both gram negative and gram positive organisms. The four microorganisms used were *Escherichia coli* , *Pseudomonas aeruginosa* , *Staphylococcus aureus* and *Bacillus subtilis.* The petridishes were thoroughly washed and sterilized. Prepared Agar media was added into sterilized petridish and allowed solidify. After solidification of media, 0.1ml of inoculum was added over it and spreaded for even distribution of organism. Here both high and low strength disks were applied for each antibiotic to be tested. The organism was reported as being sensitive if a clear zone appeared around both disks. If the zone appeared around the high concentration

alone, the organism is called moderately susceptible. If zones are taking in both the disks, the organism was considered resistant to drug. 10 µl of the sample was placed on the disk. Using the concentration of 5mg/ml and 10 mg/ml, samples were prepared in duplicate in each petridish. A standard (Amoxycillin trihydrate for antibacterial activity) was maintained with same concentration in another plate and a control having only DMSO in one plate. Then the petridishes were incubated at 37 ºC for 24 h and zones of inhibition were observed and measured.

Table No. 5: Antimicrobial activity of the newly synthesized naphtha[2,1-b]furan-thiazole derivatives.

S.No.	COMPOUND No.	ZONE OF INHIBITION(mm)			
		1*	**2****	**3*****	**4******
1	A	20	14	20	10
2	B	12	14	20	13
3	C	10	11	11	7
4	D	12	14	17	12
5	E	17	15	17	14
6	F	20	14	21	14
7	G	19	9	18	13
8	H	12	14	22	15
9	I	14	11	17	11
10	J	10	14	15	14
11	Amoxicillin	23	22	24	23

** Pseudomonas aeruginosa **Escherichia coli ***Staphylococcus aureus ****Bacillus subtilis*

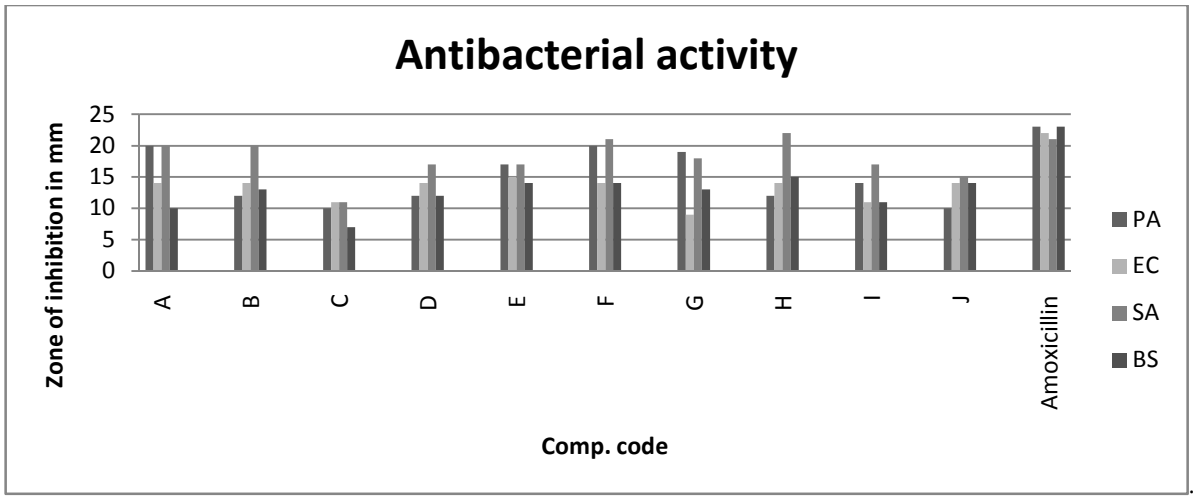


Figure 1: Effect of newly synthesized Naphtho[2,1-b]furan-thiazole derivatives on antibacterial activity.

Antitubercular activity [10]:

The anti tubercular activity of compounds were assessed against *M. tuberculosis* using Microplate Alamar Blue assay (MABA). Briefly, 200µl of sterile deionzed water was added to all outer perimeter wells of sterile 96 wells plate to minimize evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µl of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/ml. Plates were covered and sealed with parafilm and incubated at 37ºC for five days. After this time, 25µl of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted

as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink.

Table No. 6 : Antitubercular activity of the newly synthesized thiazole derivatives

Compounds	Concentration (µg/ml)									
	100	50	25	12.5	6.25	3.125	1.6	0.8	0.4	0.2
0-OH	S	S	R	R	R	R	R	R	R	R
p-OH	S	S	R	R	R	R	R	R	R	R
m-NO_2	S	S	R	R	R	R	R	R	R	R
p-NO_2	S	S	R	R	R	R	R	R	R	R

S: Sensitive R: Resistant

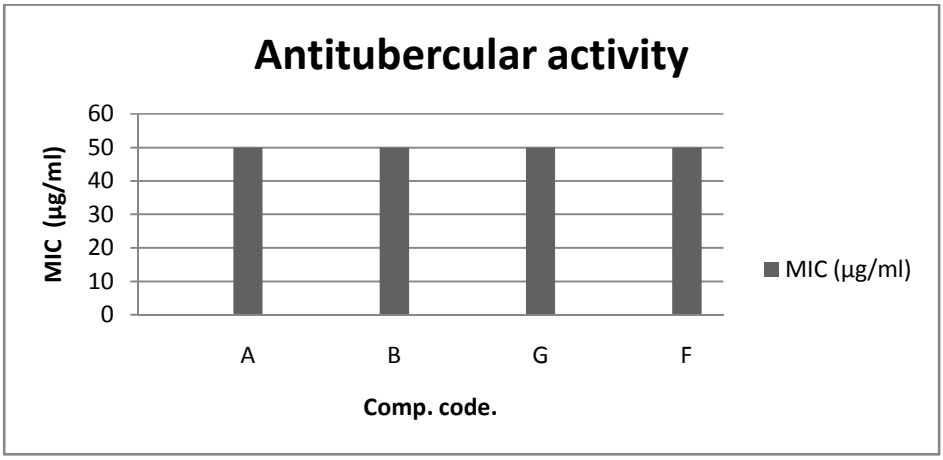


Figure no. 2: Graph showing anti-tubercular effect of newly synthesized naphtho[2,1-b]furan-thiazole derivatives.

RESULTS AND DISCUSSION

Antiulcer activity

The results of aspirin plus pylorus ligation induced model in rats suggested that the synthesized compounds with p-OH, p-Br and p-NO_2 substitution (i.e. compounds B, C and F) produced extremely significant decrease in ulcer index which is also evidenced by significant increase in % protection from ulcer when compared to the standard drug Ranitidine. The results of gastric volume determination of treated groups indicated that there was a significant decrease in the volume of gastric juice in compounds C and H. The results of gastric pH determination, of various treated groups indicated that there was a significant increase in the pH of compounds B, C, F and H..The results of free acidity, total acidity and total protein estimation of gastric juice of treated groups indicated that there was a significant decrese in the free acidity, total acidity and total proteins of the gastric juice in compounds B, C, F and H. The results of the protein estimation of gastric juice of treated groups indicated that there is a significant decrease in the total protein content of compounds B, C and F. The activity was comparable and equipotent as that of Ranitidine.

Antibacterial activity

The antibacterial activity screening suggests that among various naphtho[2,1-b]furan-thiazole derivatives 0-hydroxy, p-nitro and m-nitro showed potent activity against *P.aeruginosa*. None of

the compounds showed potent activity against *E.coli*, p-OH, 0-OH, p-nitro and vinyl compounds showed only moderate activity against E.coli. p-Cl and p-nitro were found to be highly active against *S.aureus.* Only p-Cl, p-OCH_3, vinyl and p-NO_2 were found to be moderately active against *B.subtilis*

Antitubercular activity
The compounds with 0-OH, p-OH, p-NO_2 and m-NO_2 substitution were further screened for anti-tubercular activity and all the four derivatives were found to be sensitive at a concentration of 50 and 100 µg/ml.

CONCLUSION

The compounds with p-OH, p-Br and p-NO_2 substitution have shown good antiulcer activity. Compounds with 0-OH, p-OH, m-NO_2 and p-NO_2 substitution showed potent antibacterial activity and were further screened for antitubercular activity. All the four derivatives were found to be sensitive at a concentrations of 50 and 100 ug/ml

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