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Comparitive study of antiinflammataory, analgesic and antimicrobial activity of triazole heterocycles including some nitrogen condensed and bridged heterocycles

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ABSTRACT

An attempt has been made to correlate the various biological activity of N-bridged triazole heterocylcles and to derive possible structure activity relationship among the various triazole heterocycles.

Key words:- 3-substituted-4-amino-5-mercapto-1,2,4-triazoles,ibuprofen, biological activity, triazolo thiadiazoles, hydrazino triazoles.

INTRODUCTION

Several 3-subsititued-4-amino-5-mercapto-1,2,4–triazoles, 3,4- disubstiuted-5-mercapto- 1,2,4-triazole bearing Ibuprofen moiety and their different derivatives have been selected for the comparitive study. The synthetic pathway, establishment of their structure by elemental analysis, spectroscopic studies etc have already been reported[1-4]. The biological activity of the selected few compounds have also been reported. In the presence study, detailed biological activity such as antibacterial, antifungal, antiinflammatory and analgesic activity[3-6] is carried out for all synthesized compounds by the same reported procedure and results of various activities is furnished in table 1 & 2.

The synthetic pathways of the compounds selected for study is also described

The synthesized compounds (1-41) were screened for invitro antibacterial and anti fungal activity at 50 µg/ml and 100 µg/ml concentration against the organisms *Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli and Aspergillus niger / F.oxserum* using cup plate method. DMSO was the solvent control for both antibacterial and antifungal activities. Penicillin and streptomycin were used as standard for antibacterial and griseofulvin as standard for antifungal screening. The culture media was nutrient agar and DMSO was solvent control.

The compounds 1-5,8,13-6,32 showed equipotent antibacterial activity with zone of inhibition (16-18mm, 18-21mm) while rest of the compounds screened for antibacterial activity showed moderate antibacterial activity (13-15mm and 14-18mm zone of inhibition) at 50 µg/ml and 100 µg/ml concentration. The standard drugs penicillin and streptomycin showed 17-21mm and 17-22mm zone of inhibition against different organisms. However the antifungal screening results revealed hat the compounds exhibit weak activity in comparison with the standard griseofulvin.

The antibacterial screening of the compounds revealed that the parent triazoles derived from different aryl and aryloxy acid bearing ibuprofen moiety at position 4 possess marked antibacterial activity. When the same type of triazoles was constructed from ibuprofen moiety substituted at 3rd position having amino and mercapto groups at position 4 and 5 respectively furnished 3-[(4'-isobutyl phenyl)ethyl]-4-amino-5-mercapto triazoles(16) and was then converted to get 3,5-disubstituted-6-thiano-1,2,4-triazolo (3,4-b)(1,3,4)-thiadiazoles(17-31) and 6,6'-bis-[3-(4'-isobutyl phenyl)ethyl]-1,2,4-triazolo(3,4-b0(1,3,4)-thiadiazole derivatives (32,33 and 34).These compounds however showed weak to moderate antibacterial activity and weak antifungal activity when compared with their respective standards against all the pathogenic organisms selected for study. The introduction of ibuprofen moiety at position 3 in the series of compounds (17-34) failed to enhance the antibacterial and antifungal activity of the compounds under investigation. Thus in these series of compounds thiadiazole moiety which possesses potent anti bacterial and antifungal activity when fused with triazole to get triazole thiones and bis-triazolo thiadiazoles failed to exhibit increased antibacterial activity.

Perhaps the presence of bulky substituents on triazolo thiadiazole system and in turn their stearic hinderance may be the possible reasons for suppression of the potent activities of triazolo thiadiazole type of system.

Further modification and taking care that no bulky groups on triazolo thiadiazole ring system and compactness of the fused triazole and thiadiazole moieties may help in enhancing the activity. The active derivatives may be useful as antibacterial agents after careful study of the toxicity of the compounds and may be used in the form of ointments, gels and sprays.

Antibacterial and antifungal screening of (35-41) revealed that the compounds did not exhibit encouraging results and they possess only weak activity. Thus conversion of triazole(16) to its hydrazino triazole did not yield potent compounds much against certain reported literature of the compounds having this type of moiety.

Anti-inflammatory screening

The compounds synthesized were tested for their antiinflammatory activity using rat hind paw edema method of winter-et-al modified by Dhawan and Srimmal

The compounds 16,17,19,23,32,33,34, 35,36,39 showed marked activity in comparison with the standard ibuprofen. The compounds 23,35,39 showed excellent activity even superior than the standard and rest of the compounds showed almost equipotent activity with the standard compounds 33,34,37,38,40,41 showed the inhibition in the range 55 to 65%(table 1).

The yields of the compounds are between 58-85%

The antiinflammatory activity few compounds screened revealed that the triazolo, thiadiazole thiones, triazole-thiadiazoles and hydrazino triazoles exhibited much enhanced activity in comparison with the parent triazole. Perhaps triazolo thiadiazole ring system in triazolo thiadiazole derivatives and hydrazine group in hydrazino-triazoles may help in enhancing the antiinflammatory activity. Phenyl, 4-chloro phenyl, 4-amino phenyl, phenoxy, 2-methyl phenoxy, 4-chloro phenoxy groups present in triazole derivatives contribute much towards the enhancement of antiinflammatory activity. The presence of the substituted groups on phenyl or phenoxy moiety has less influence on antiinflammatory activity. The compounds which failed to show better antibacterial and antifungal activity have exhibited marked antiinflammatory activity, justifying the fact that fusion of two heterocyclic moieties generally enhance the biological activity of the fused systems.

The compounds were also screened for analgesic activity using Eddy's hot plate technique. Mice of either sex weighing between 25-35g were used for the study and ibuprofen was used as standard. The % of analgesic activity (PPA) was calculated by the following formula.

$$PPA=T_2/T_1X100$$

T_1 is the reaction time before treatment.
T_2 is the reaction time after treatment.

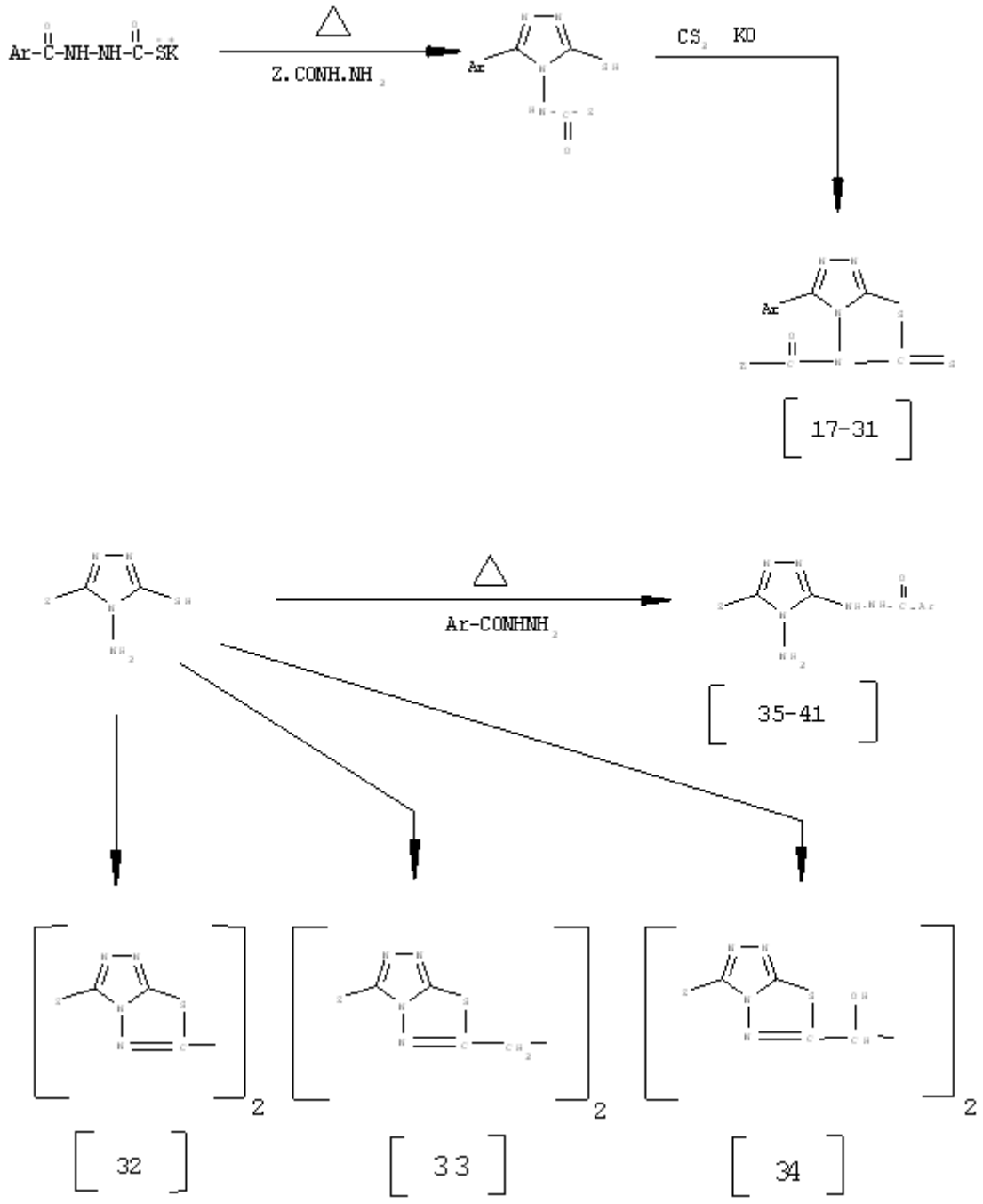
Table 1: Characteristic data and pharmacological activity of triazole derivative 1-41

Compound No.	Ar-z	Melting point	Anti inflammatory activity %	Analgesic activity%
1	phenyl	170	38	143
2	2-chloro phenyl	260	36	156
3	4-chloro phenyl	241	42	161
4	4-nitro phenyl	270	40	140
5	3,5-dinitro phenyl	244	41	152
6	2-amino phenyl	240	34	134
7	4-amino phenyl	250	36	161
8	phenoxy methyl	270	38	152
9	2-methyl phenoxy methyl	284	44	128
10	3-methyl phenoxy methyl	270	36	108
11	4-methyl phenoxy methyl	285	39	117
12	4-amino phenoxy methyl	190	43	126
13	4-nitro phenoxy methyl	259	39	152
14	1-naphthoxy methyl	156	34	142
15	2-napthoxy methyl	135	38	154
16	Z	96	54	192
17	phenyl	95	76.38	250
18	2-chloro phenyl	84	52	161
19	4-chloro phenyl	230	76.92	248
20	4-nitro phenyl	241	50	145
21	3,5-dinitro phenyl	250	-	-
22	2-amino phenyl	92	-	-
23	4-amino phenyl	230	80.9	238
24	phenoxy methyl	140	54	140
25	2-methyl phenoxy methyl	195	49	143
26	3-methyl phenoxy methyl	108	42	134
27	4-methyl phenoxy methyl	120	45	126.8
28	4-amino phenoxy methyl	250	-	-
29	4-nitro phenoxy methyl	210	-	-
30	1-napthoxy methyl	115	44	124
31	2-napthoxy methyl	120	46	128
32	Z	130	60	158
33	Z	103	62	176
34	Z	115	64	187
35	phenoxy	190	88	268
36	2-methyl phenoxy	160	79	228
37	3-methyl phenoxy	165	65	213
38	4-methyl phenoxy	170	62	203
39	4-chloro phenoxy methyl	130	88.46	230
40	3-chloro phenoxy methyl	103	64	1.88
41	benzyl	115	61	172
	Ibuprofen		76.92%	256

Table 2: Antibacterial and antifungal activity of triazole heterocycles

Compound	Antibacterial activity zone of inhibition in mm and concentration in µg/m								Antifungal activity zone of inhibition in mm and concentration in µg/ml	
	B.subtilis		*S.aureus*		*P.aeruginosa*		*E.coli*		*F. oxserum*	
	50	100	50	100	50	100	50	100	50	100
1	16	20	17	20	15	19	18	21	08	12
2	17	21	17	21	14	18	18	21	11	14
3	18	20	17	20	14	19	18	20	12	14
4	17	20	16	19	13	16	17	20	10	14
5	17	20	17	20	14	17	17	20	11	13
6	15	18	16	19	14	18	18	21	10	13
7	15	19	16	19	15	19	16	19	09	12
8	16	19	16	19	15	19	16	19	08	12
9	14	18	15	18	13	18	16	20	10	14
10	15	18	15	18	13	18	15	19	08	11
11	15	18	13	16	12	15	14	18	09	12
12	14	17	12	16	13	16	14	19	08	12
13	17	20	15	18	14	17	16	19	10	14
14	16	19	15	18	14	16	15	18	09	14
15	17	20	16	20	15	18	16	20	10	13
16	16	19	16	19	15	19	17	20	11	13
17	13	17	10	14	08	13	08	11	08	11
18	13	16	11	14	08	12	07	11	07	10
19	14	17	12	17	08	13	09	12	09	13
20	14	17	12	16	09	14	07	11	07	12
21	13	16	11	15	10	14	07	11	08	12
22	13	15	11	15	19	15	07	11	06	10
23	14	17	13	16	10	14	06	11	07	11
24	13	16	12	15	11	16	09	12	08	12
25	13	16	10	14	11	15	08	13	08	12
26	13	15	10	13	11	15	08	13	07	11
27	14	18	15	18	13	18	16	20	09	12
28	15	18	13	16	12	15	14	18	08	11
29	14	17	12	17	08	13	08	11	09	13
30	14	17	13	16	10	14	06	11	06	10
31	15	17	16	19	15	19	16	19	10	13
32	16	19	16	19	15	19	16	19	09	13
33	13	15	11	15	11	15	06	11	08	12
34	13	16	10	14	11	15	08	13	08	12
35	13	16	12	15	11	16	09	12	07	11
36	14	17	12	16	09	14	07	11	07	12
37	13	17	10	14	08	13	11	08	08	11
38	13	16	11	14	08	12	07	11	07	10
39	12	15	10	13	11	15	08	13	07	11
40	13	15	10	13	11	15	08	12	07	11
41	13	15	11	15	11	15	06	11	08	12
Pencillin	17	21	17	20	18	21	17	22		
Streptomycin	18	20	18	21	17	20	18	21		
Griseofulvin									16	19

The study of analgesic activity of triazole derivatives revealed that the compounds showed moderate to significant activity. The compounds 19, 32, 35 and 39 showed significant analgesic activity while the rest of the compounds showed weak to moderate activity compared with the standard ibuprofen. Although the test compounds possess significant antiinflammatory and analgesic activities,



Scheme 1

their efficacy is not enough to develop them into a clinically useful agent. But the active compounds really need a special attention as some of the compounds exhibited much superior activity than the standard used for comparison.

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