ANTI-INFLAMMATORY ACTIVITY OF INDANYLTETRAZOLE DERIVATIVES

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ABSTRACT

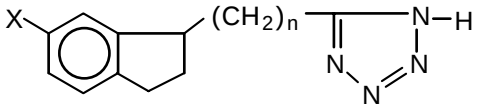
A number of indanyl tetrazolederivatives namely 5-(6′-chloroindan-1′-yl)tetrazole (CIT), 5-(6′-bromoindan-1′-yl)tetrazole (BIT), 5-(6′-chloroindan-1′-yl)methyltetrazole (CIMT), 5-(6′-bromoindan-1′-yl)methyl-tetrazole (BIMT) were evaluated for the anti-inflammatory activity in carragennan induced rat paw edema in Swiss *albino* Wister rats for 24-hour period at the dose of 100 mg/kg of body weight by intraperitoneal route where phenylbutazone (PBZ) was used as the standard. All of these compounds exhibited inhibition on rat paw edema with peak actions observed following 3 hours after administration. Moreover, compounds CIMT and BIMT were further evaluated at dose of 50 mg/kg of body weight. Among the compounds, CIMT showed higher activity than others and was very close to standard phenylbutazone.

Keywords: Indanyltetrazoles, anti-inflammatory activity, phenylbutazone, carragennan.

INTRODUCTION

The most common serious drawback of all analgesic and anti-inflammatory drugs is that they cause serious acidity problems which limits their use in many cases. As a result most of the patients were unable to continue these drugs for their ailment from diseases. To circumvent the acidity or gastrointestinal effects of anti-inflammatory drugs several newer templates or leads were selected which include indole nucleus, arylalkyl acid nucleus, pyrazolone, indan etc. and attempt has been taken to discover novel anti-inflammatory agent without or less gastrointestinal effects (Winter C.A. *et al*, 1963 and Remington, 1990). These nuclei were undergone some structural or molecular modifications either by introducing functional groups or ring fusion. Both the modifications resulted many promising anti-inflammatory agents. It was already established that tetrazole, an aromatic azapyrrole group, is metabolically stable (Fidgor *et al, 1967)* and has acidic characteristics closely similar to that of the carboxylic group (Herbst, 1956). At the same time it has been reported that anti-inflammatory and related biological activities have been improved or abolished by the substitution of a 5-tetrazole group in place of carboxyl function (Ganellin, 1967). In this context a number of indanyltetrazoles have been synthesized and encouraging anti-inflammatory activity has been noted (Roy *et al.,* 1983, Ray *et al.*, 1990, and Roy *et al.*, 1985. The remarkable achievements were 5-(6′-methoxyindan-1′-yl)tetrazole and 5-(5′,6′-dimethoxy-indan-1′-yl)tetrazole.

According to the Burger, 1970, many medicinal chemists look on halogen substitution, especially chlorination, as a reasonable means of stepping up the activity. In studies, significant analgesic activity has been observed in compounds 5-(6′-chloroindan-1′-yl)tetrazole (CIT), 5-(6′-bromoindan-1′-yl)tetrazole (BIT), 5-(6′-chloroindan-1′-yl)methyltetrazole (CIMT) and 5-(6′-bromoindan-1′-yl)methyltetrazole (BIMT) (Bachar, S.C., 2004). So these four compounds have been synthesized in order to observe the anti-inflammatory activities. The compounds are:



Where,

5-(6′-chloroindan-1′-yl)tetrazole (CIT)	X=Cl, n=0
5-(6′-bromoindan-1′-yl)tetrazole (BIT)	X=Br, n=0
5-(6′-chloroindan-1′-yl)methyltetrazole (CIMT)	X=Cl, n=1
5-(6′-bromoindan-1′-yl)methyltetrazole (BIMT)	X=Br, n=1

We herein report the anti-inflammatory activity of the indanyltetrazole derivatives (CIT, BIT, CIMT and BIMT) in Swiss *albino* Wister rats.

EXPERIMENTAL

Study design

During the study (Winter, 1962), the animals were weighed and those with average weight 130-170 gm were taken. They were randomly divided into ten groups consisted of 5 rats and were named as Group-CIT-100, Group-BIT-100, Group-CIMT-100, Group-BIMT-100, PBZ-100, Control-100, Group-CIMT-50, Group-BIMT 50, Group-PBZ-50 and Control-50. In the first study, Group-CIT-100, Group-BIT-100, Group-CIMT-100 and Group-BIMT-100 received intraperitonially (i.p.) the test compounds 5-(6′-chloroindan-1′-yl)tetrazole (CIT), 5-(6′-bromoindan-1′-yl)tetrazole (BIT), 5-(6′-chloroindan-1′-yl)methyltetrazole (CIMT) and 5-(6′-bromoindan-1′-

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Table 1: *In vivo* anti-inflammatory activity study of 5-(6′-chloroindan-1′-yl)tetrazole (CIT) and 5-(6′-bromoindan-1′-yl)tetrazole (BIT), 5-(6′-chloroindan-1′-yl)methyltetrazole (CIMT) and 5-(6′-bromoindan-1′-yl)methyltetrazole (BIMT) at 100 mg/kg dose level

Group	Percentage change in rat paw volumes (x ± SE) at 100 mg/kg dose level				
	1 hour	2 hours	3 hours	4 hours	24 hours
Group-CIT-100	82.5 ± 1.90 [b] (14.77)* t = 4.41	94.0 ± 2.62 [b] (18.12) t = 4.87	89.7 ± 2.15 [a] (26.05) t = 10.99	79.9 ± 3.63 [b] (19.66) t = 4.90	57.5 ± 2.15 [d] (11.94) t = 2.62
Group-BIT-100	79.2 ± 3.35 [b] (18.18) t = 4.13	89.7 ± 4.67 [b] (21.86) t = 4.86	92.2 ± 1.82 [a] (23.99) t = 11.03	81.2 ± 4.24 [b] (18.15) t = 3.97	59.3 ± 2.33 [e] (9.19) t = 1.93
Group-CIMT-100	80.4 ± 2.29 [b] (16.94) t = 4.70	76.6 ± 1.84 [a] (33.28) t = 13.28	72.8 ± 2.10 [a] (39.98) t = 17.09	64.3 ± 1.47 [a] (35.18) t = 15.94	52.5 ± 1.82 [b] (19.60) t = 4.66
Group-BIMT-100	78.4 ± 3.86 [b] (19.01) t = 3.94	83.1 ± 4.37 [a] (27.61) t = 6.46	81.2 ± 2.20 [a] (33.06) t = 13.76	67.4 ± 1.99 [a] (32.06) t = 12.39	58.2 ± 1.58 [d] (10.87) t = 2.73
Group-PBZ-100	69.8 ± 4.87 [b] (27.89) t = 4.88	68.4 ± 1.87 [a] (40.42) t = 16.03	70.7 ± 1.58 [a] (41.71) t = 20.41	63.5 ± 2.13 [a] (35.99) t = 13.34	50.8 ± 4.02 [c] (22.11) t = 3.21
Control-100	96.8 ± 2.63	114.8 ± 2.21	121.3 ± 1.91	99.2 ± 1.62	65.3 ± 2.06

*Figures in parentheses indicate percent inhibition of rat paw edema

[a-d] Probability values (calculated as compared to control using student's t-test): a<0.001, b<0.01, c<0.02, d<0.05

[e]not significant. Values are average of five animals.

yl)methyltetrazole (BIMT) respectively at the doses of 100 mg/kg of body weight. Group-PBZ-100 received phenylbutazone (PBZ) at dose of 100 mg/kg and was treated as standard. At the same time, Control-100 received saline solution and was treated as the control.

In the next experiment, Group-CIMT-50 and Group-BIMT-50 received intraperitonially (i.p.) the 5-(6′-chloroindan-1′-yl)methyltetrazole (CIMT) and 5-(6′-bromoindan-1′-yl)methyltetrazole (BIMT) respectively at the dose of 50 mg/kg of body weight. Group-PBZ-50 received phenyl butazone (PBZ) at the dose of 50 mg/kg and was treated as the standard. At the same time, Control-50 received saline solution and was treated as control. After half an hour of drug administration 1% carrageenan solution was injected into the subplanter surface of the right hind-paw of each rat of each group.

Observations

The paw volumes were measured by mercury displacement as viewed by traveling microscope at 1, 2, 3, 4 and 24 hours of the administration of the drug and test compounds. Average percentage inhibition of rat paw edema was calculated as the difference between the paw volumes of control and drugs 5-(6′-chloroindan-1′-yl)tetrazole (CIT), 5-(6′-bromoindan-1′-yl)tetrazole (BIT), 5-(6′-chloroindan-1′-yl)methyltetrazole (CIMT) and 5-(6′-bromoindan-1′-yl)methyltetrazole (BIMT) as the percentage of volume of control (tables 1 and 2).

RESULTS AND DISCUSSION

Anti-inflammatory activity

The results of the anti-inflammatory activity in carrageenan-induced rat paw edema test at the dose of 100 mg/kg of body weight (table 1) showed that 5-(6′-chloroindan-1′-yl)methyltetrazole (CIMT) and 5-(6′-bromoindan-1′-yl)methyltetrazole (BIMT) showed better activity as compared to the 5-(6′-chloroindan-1′-yl)tetrazole (CIT) and 5-(6′-bromoindan-1′-yl)tetrazole (BIT). The percentage inhibitions produced by CIT, BIT, CIMT and BIMT were compared with that of phenylbutazone (table 1 and graph 1). The results were very close to that of standard.

The compounds 5-(6′-chloroindan-1′-yl)methyltetrazole (CIMT) and 5-(6′-bromoindan-1′-yl)methyltetrazole (BIMT) were further studied at the dose of 50 mg/kg, where promising activity was exhibited by CIMT. The activity of BIMT was also significant but not to the same degree of CIMT (table 2 and graph 2).

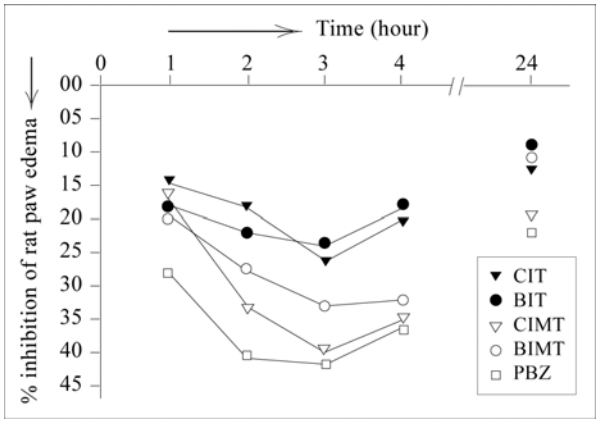
CONCLUSION

It can be concluded that all the synthesized indanyl tetrazole derivatives exhibited anti-inflammatory activity. But the activity of 5-(6′-chloroindan-1′-yl) methyl-tetrazole (CIMT) was more promising than others. The

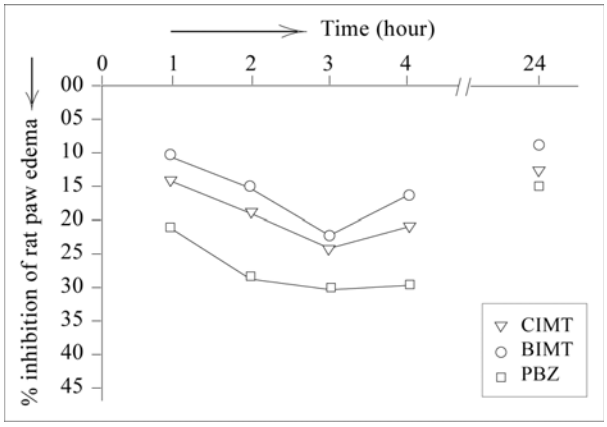
Table 2: *In vivo* anti-inflammatory activity study of 5-(6′-chloroindan-1′-yl)methyltetrazoles (CIMT) and 5-(6′-bromoindan-1′-yl)methyltetrazoles (BIMT) at 50 mg/kg dose level

Group	Percentage change in rat paw volumes (x ± SE) at 50 mg/kg dose level				
	1 hour	2 hours	3 hours	4 hours	24 hours
Group-CIMT-50	75.5 ± 2.20 [b] (12.62)* t = 4.13	88.4 ± 3.62 [b] (17.84) t = 4.99	91.9 ± 20.20 [a] (24.92) t = 9.61	82.8 ± 2.68 [a] (20.07) t = 5.47	56.6 ± 1.92 [c] (12.11) t = 3.09
Group-BIMT-50	77.2 ± 1.87 [b] (10.65) t = 3.88	92.4 ± 3.12 [b] (14.12) t = 4.49	94.9 ± 2.08 [a] (22.47) t = 8.56	86.4 ± 2.40 [b] (16.60) t = 4.76	58.9 ± 2.76 [e] (8.54) t = 1.71
Group-PBZ-50	68.1 ± 3.69 [b] (21.18) t = 4.61	77.2 ± 1.77 [a] (28.25) t = 13.81	85.7 ± 2.15 [a] (29.98) t = 11.26	72.4 ± 2.31 [a] (30.11) t = 8.78	54.7 ± 1.78 [b] (15.06) t = 4.01
Control-50	86.4 ± 1.46	107.6 ± 1.31	122.4 ± 2.45	103.6 ± 2.70	64.4 ± 1.64

*Figures in parentheses indicate percent inhibition of rat paw edema
[a-c]Probability values (calculated as compared to control using student's t-test): a<0.001, b<0.01, c<0.02
[e]not significant. Values are average of five animals



Graph 1: *In vivo* anti-inflammatory activity study of 5-(6′-chloroindan-1′-yl)tetrazole (CIT) and 5-(6′-bromoindan-1′-yl)tetrazole (BIT), 5-(6′-chloroindan-1′-yl)methyltetrazole (CIMT) and 5-(6′-bromoindan-1′-yl)methyltetrazole (BIMT) when given at a dose of 100 mg/kg of body weight.



Graph 2: *In vivo* anti-inflammatory activity study of 5-(6′-chloroindan-1′-yl)methyltetrazole (CIMT) and 5-(6′-bromoindan-1′-yl)methyltetrazole (BIMT) when given at a dose of 50 mg/kg of body weight.

study related to the synthesis of newer templates of anti-inflammatory agents is on progress.

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