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Research Article

Synthesis and evaluation of 2, 2'-bis-7-substituted-[1,3,4]thiadiazolo-[2,3-b]quinazolin-5-one and screened for anti-inflammatory activity

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Abstract

A series of 2, 2'-bis-7-substituted-[1,3,4] thiadiazolo-[2,3-b] quinazolin-5-one were synthesized by action of 3-amino-2-mercaptoquinazolinone-4(3H)-one with various dicarboxilic acids in the presence of phosphorousoxy chloride. The newly synthesized compounds have been characterized by their analytical and spectral (IR, H^1NMR and Mass) properties. Further, they have been screened for their anti-inflammatory (*in vitro* and *in vivo*) activities by standard method. Results of the activities reveal that, compounds exhibited significant anti-inflammatory activities.

Keywords: Quinazolinones, Thiadiazoloquinazolinone, Anti-inflammatory activity, Bovin albumin.

1. Introduction

Quinazoline is a bicyclic compound earlier known as benzo-1, 3-diazine was first prepared in the laboratory by Gabriel in 1903 although one of its derivative was known much earlier [1].

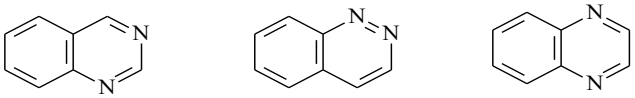

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Figure 1: Structure Quinazoline

The name quinazolinone (German: Chinazolin) was first proposed for its compound by Weddige, on observing that this was isomeric with the compounds cinoline and quinaoxaline. The 'oxo' derivative of '**quinazoline**' is suffixed by 'one', that is **'quinazolinone'**. Quinazolinones and several of their derivatives have been found to be of greater interest in view of their varied biological and pharmacological properties. Quinazolines and their derivatives have been reported to possess varied pharmacological properties as Chemotherapeutic agents like: Antibacterial, Antifungal, Antiviral, Anthelmintic, Amoebicide, Antimalarial, etc. 2-Cyanoquinazolin-4(3H)-one was the first quinazolin derivative prepared by Griess [2].

Quinazolinones and several of their derivatives have been found to be of greater interest in view of their varied biological and pharmacological properties. The prominence enthused several chemists and medicinal chemists to prepare newer and newer quinazolinones by different synthetic routes while incorporating a variety of known pharmacophores into their molecular systems and evaluating them for their possible biological and pharmacological properties.

The present survey aims to bring out the various routes that are intended to achieve the synthesis of quinazolinones and their derivatives of specific biological and pharmacological importance.

1.1 Aims and objectives

Having witnessed from literature, it is thought useful to synthesize and characterize some new quinazolinone fused heterocycles; for this purpose 3-amino-2-mercapto-4(3H)-quinazolinone and their nuclear substituted analogous are selected as SYNTHONS. It is

aimed to build-up some biologically and pharmacologically potent heterocycles while making use of amino and mercapto groups of the synthon. The present work is thus designed to achieve the synthesis of 2,2'-bis-7-substituted[1,3,4]thiadiazolo[2,3-b] quinazolin-5-one. In view of the associated biological and pharmacological properties of these heterocyclics, it is planned to screen them for their possible anti-inflammatory activity, in conjunction with quinazolinones.

2. Methodology

2.1 Present work

It could be noted from the literature the heterofused quinazolinones in general and the fused thiadiazoloquinazolones, in specific are associated with varied biological and pharmacological properties. It is also evident that relatively a very few compounds are reported so far in spite of their significance.

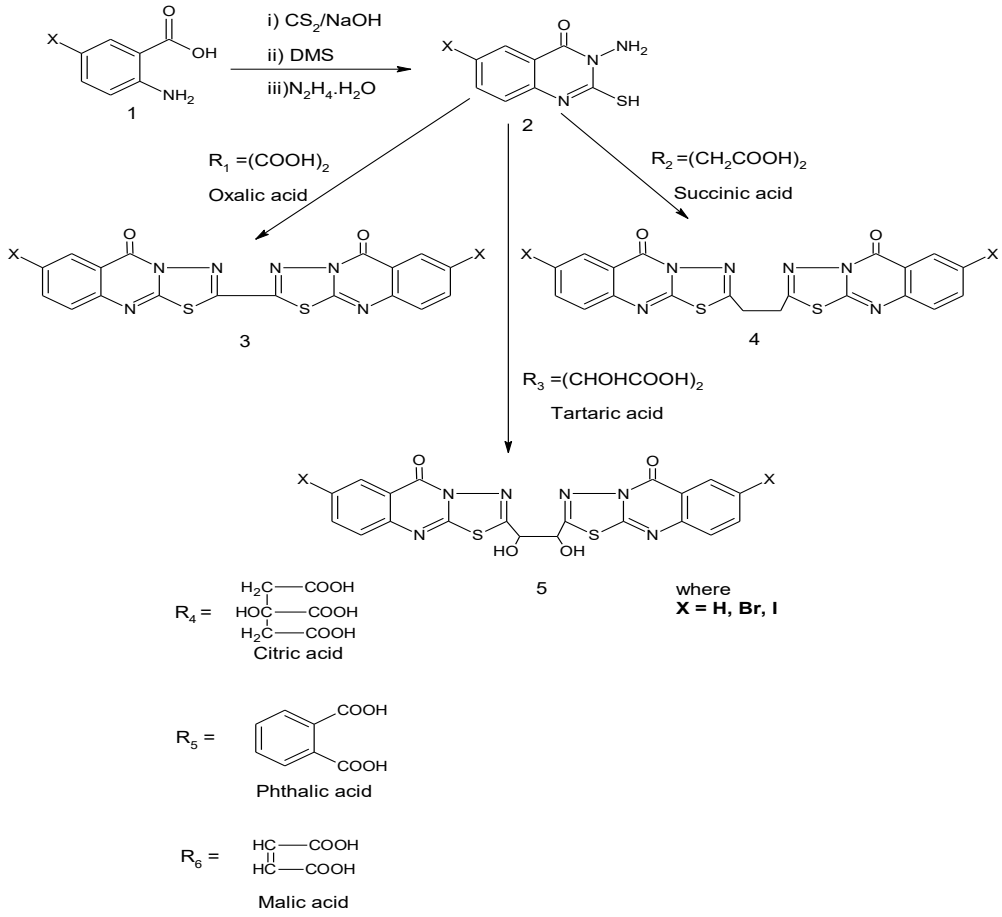
Therefore, in continuation of our work on quinazolinones and associated thiadiazoles, it has been considered worth-while to effect the synthesis of some new fused thiadiazoloquinazolinones by making use of 3-amino-2-mercaptoquina- zolinones as synthons, with a view to evaluate them for their biological potency.

For this purpose, the required three different 3-amino-2-mercaptoquinazolin-4(3H)ones (2, X=H, Br or I) will be prepared from their respective 2-amino benzoic acids (1) first by reacting with a carbon disulphide in presence of an alkali sodium hydroxide, secondly with dimethyl sulphate followed by the reaction with hydrogen hydrate adopting standard procedure. Each of the 3-amino-2-mercaptoquinazoline-4(3H)-ones have been identified by their literature melting points and I.R. spectral data.[5]

Each of these three 3-amino-2-mercapto-quinazolinones, has been subjected to the following cyclocondensation 2.2 reactions, as depicted in **Scheme-I.**

2.2 Action of Aromatic and Aliphatic Dicarboxylic Acids on 3-Amino-2-mercapto-4(3H)quinazolinones:

2,2'-bis-7-substituted-[1,3,4]thiadiazolo[2,3-b]quinazolin-5(4H)ones(3,4,5) have been obtained by reaction of 3-amino-2-mercaptoquinazolin-4(3H)-ones and aromatic or aliphatic dicarboxilic acid (R_1, R_2, R_3, R_4 & R_5) by heating under reflux in presence of phosphorous oxychloride. The newly synthesized compounds have been confirmed by their analytical and spectral (IR, H^1NMR and Mass) data. The newly synthesised series of compounds have been subjected to the anti-inflammatory activity by appropriate standard methods. [3]



Scheme – I

2.3 Anti-inflammatory activity (*in vitro* model)

Many *in vitro* assays, each based on a specific biochemical or cellular mechanism have been developed for the initial screening of the anti-inflammatory compounds.

A number of anti-inflammatory drugs are known to inhibit the denaturation of proteins as an *in vitro* screening model for anti-inflammatory compounds.

The synthesized compounds are screened for anti-inflammatory activity by using inhibition of albumin denaturation technique, which was studied according to Muzushima and Kabayashi with slight modification.

The standard drug and test compounds were dissolved in minimum amount of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solutions was less than 2.0%. Test solution (1 ml) containing different conc. of drugs was mixed with 1 ml of 1% mM albumin solution in phosphate buffer and incubated at $27^0 \pm 1^0$C in BOD incubator for 15 min. Denaturation was induced by keeping the reaction mixture at $60^0 \pm 1^0$C water bath for 10 min. After cooling the turbidity was measured at 660 nm (UV-Visible Spectrophotometer SL-159, Elico India Ltd.). Percentage of inhibition of denaturation was calculated from control where no drug was added. [6] Each experiment was done in triplicate and average was taken. The ibuprofen was used as standard drug. Results are tabulated in Table 1.

$$\% \text{ of inhibition} = \left(\frac{Vt - 1}{Vc} \right) \times 100$$

Where, vt = mean absorbance value of test group.

vc = mean absorbance value of control group.

2.4 Anti-inflammatory activity by carrageenan induced rat hind paw edema method (*in vivo* model)

Animals were divided into control, standard, different test groups comprising of five animals in each group. They were fasted overnight with free access to water before experiment. In all groups, acute inflammation was produced by subplanter injection of 0.1 ml of freshly prepared 1% suspension of carrageenan in the right hind paw of the rats and paw of the rats and paw volume was measured plethysmometrically at 0 hr and 3 hrs after carrageenan injection. The test compounds (50 mg/kg) was administered orally, standard group was treated with ibuprofen (50 mg/kg) orally 1 hr. before by injection and control group received only vehicle. Mean difference in paw volume was measured statically by student 't' test in dunnett and percentage inhibition was calculated by following formula [7]:

$$\% \text{ inhibition of edema} = \left(\frac{Vc - Vt}{Vc} \right) \times 100$$

Where, Vt = mean paw volume of test group.

Vc = mean paw volume of control group.

3. Results

Results for anti-inflammatory activity (*in vitro* model) are given in the Table 1,

Table 1: Anti-inflammatory activity (*in vitro* model)

S. No.	Compound code	Absorbance value (Mean ± SE)	Inhibition of denaturation (in%)
1	Control	0.046 ± 0.00057	--
2	Standard (Ibuprofen)	0.08033 ± 0.00033	74.63 %
3	DK-1	0.06166 ± 0.00066	34.04 %
4	DK-2	0.06833 ± 0.00033	48.54 %
5	DK-3	0.067 ± 0.0010	45.65 %
6	DK-4	0.08 ± 0.0010	73.91 %
7	DK-5	0.06066 ± 0.00088	31.87 %
8	DK-6	0.07866 ± 0.00066	71 %
9	DK-7	0.05133 ± 0.00066	11.59 %
10	DK-8	0.058 ± 0.000	26.09 %
11	DK-9	0.05866 ± 0.00033	27.52 %
12	DK-10	0.07833 ± 0.00033	70.28 %
13	DK-11	0.058 ± 0.00011	26.09 %
14	DK-12	0.079 ± 0.00057	71.74 %
15	DK-13	0.07933 ± 0.00033	72.46 %
16	DK-14	0.065 ± 0.000	41.30 %
17	DK-15	0.05766 ± 0.00033	25.35 %
18	DK-16	0.059 ± 0.00057	28.26 %
19	DK-17	0.04833 ± 0.00033	5.07 %
20	DK-18	0.058 ± 0.00115	26.09 %

Results for anti-inflammatory activity (*in vivo* model) are given in the Table 2

Table 2: Anti-inflammatory activity (*in-vivo model*)

S. No.	Compound code	Dose (mg/kg)	Mean difference in Paw volume ± SE after 3 hr. (ml)	Percentage of inhibition
1	Control	--	3.59 ± 0.057	--
2	Standard (Ibuprofen)	50	1.05 ± 0.029***	70.75 %
3	DK-4	50	1.19 ± 0.5788***	66.85 %
4	DK-6	50	1.89 ± 0.0696***	47.35 %
5	DK-10	50	2.01 ± 0.0894***	44.01 %
6	DK-12	50	1.80 ± 0.0758***	49.86 %
7	DK-13	50	1.70 ± 0.9922***	52.64 %

**P<0.01, ***P<0.001 when compared to control group

4. Discussion

4.1 Anti-inflammatory activity (*in vitro* model)

Synthesized compounds of 2, 2'-bis-7-substituted-[1,3,4]-thiadiazolo-[2,3-b]-quinazolin-5-ones have been evaluated for anti-inflammatory activity (*in-vitro*).

The results are presented in Table 1 reveals that some of compound promisingly inhibits albumin denaturation in comparison with standard drugs; ibuprofen exhibited 74.63% inhibition of albumin denaturation.

However eight out of eighteen compounds more than 40% having inhibition of albumin denaturation. Out of that DK-2, DK-3, DK-4, DK-6, DK-10, DK-12, DK-13 and DK-14 showed 48.54%, 45.65%, 73.91%, 71%, 70.28%, 71.74%, 72.46% and 41.30% inhibition of albumin denaturation.

4.2 Anti-inflammatory activity (*in vivo* model)

The selected compounds have been evaluated for anti-inflammatory activity by carrageenan induced rat hind paw edema method compounds, which have been found more significant anti-inflammatory activity by in-vitro model. The results are presented in Table 2; compared with standard drug ibuprofen showed significant anti-inflammatory activity.

The tested compounds DK-4 (66.85%), DK-6 (47.35%), DK-10 (44.01%), DK-12 (49.86%) and DK-13 (52.64%) showed significant anti-inflammatory activity, compare to standard ibuprofen (70.75%).

From this it is concluded that one of the tested compounds have shown anti-inflammatory activity close to standard ibuprofen.

Reference

[1]. Pathak US, Alagarsamy V. Synthesis and Pharmacological Investigation of some 2-Substituted [1, 3, 4] Thiadiazolo [2, 3,-b] Quinazolin-5 (4H)-Ones as Antihypertensive Agents. *Indian Drugs-Bombay-*. 2000; 37(1):51-5.

[2]. Alagarsamy V, Pathak US, Goyal RK. Synthesis and Evaluation of Some Novel 2-Mercapto-3-(Substituted methylamino) Quinazolin-4 (3H)-Ones as Analgesic, Antiinflammatory and Antibacterial Agents. *Indian Journal of Pharmaceutical Sciences*. 2000; 62(1):63.

[3]. Bhaskar Rao A, Sisodia P, Sattur PB. Inhibition of heat-induced denaturation of human serum albumin by anti-inflammatory drugs. *Ind J Pharmacol* 1985; 17: 236-237.

[4]. Sushma Drabu, Arpana Rana, Harish Kumar. Synthesis, anti-inflammatory, ulcerogenic and antibacterial activities of 1,3,5-trisubstituted pyrazolines. *Ind J Hetero Chem* 2007; 16: 399-400.

[5]. Mohd Amir, Shikha Kumar. Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of 3,5-dimethyl pyrazoles, 3-methyl pyrazol-5-ones and 3,5-disubstituted pyrazolines. *Ind J Chem* 2005; 44B: 2532-2537.

[6]. Averineni Ravi Kumar, Subbu Rathinam KM, Prabakar G. Adv *Pharmacol Toxicol* 2006; 7(3): 13-16.

[7]. Kulkarni SK. Hand book of experimental pharmacology. III[rd] ed. Vallabha Prakashan Delhi. 2005: 127-133.