SYNTHESIS AND BIOLOGICAL ACTIVITIES OF N^4[N-(6,8-DIBROMO-2-METHYL-3-QUINAZOLIN-4(3H)-ONYL)ACETAMIDO]-N^1-SUBSTITUTED SULPHANILAMIDES.

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ABSTRACT

Eight new N^4[N-(6,8-dibromo-2-methyl-3-quinazolin-4(3H)-onyl)acetamido]-N^1-substituted sulphanilamides were synthesized, characterized and screened for their antibacterial, analgesic and anti-inflammatory activities. Some compounds have been proved to exhibit promising analgesic and anti-inflammatory activities.

INTRODUCTION

QUINAZOLINONES have been reported to possess analgesic and anti-inflammatory properties[1-3]. The biological efficacy of sulphanilamides is also well known[4]. In continuation of our work on quinazolinones[5-7], we report, the synthesis and biological activities of some N^4[N-(6,8-dibromo-2-methyl-3-quinazolin-4(3H)-onyl) acetamido]-N^1-substituted sulphanilamides. The title compounds have been synthesized by the reaction of 3-chloroacetamido-6,8-dibromo-2-methyl-quinazolin-4(3H)-one with various substituted sulphanilamides. The compounds were screened for their antibacterial, analgesic and anti-inflammatory activities.

MATERIALS AND METHODS

The purity of the compounds was checked by TLC on silicagel G. Melting points were determined in open capillaries using Toshniwal melting point apparatus and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on Perkin-Elmer infracord-283 spectrophotometer in nujol mull, 60 MHz NMR on Varian spectrophotometer using TMS as the internal reference and Mass on a CEC-2-110B double focussing spectrometer using direct inlet system.

3-Amino-6,8-dibromo-2-methyl-quinazolin-4(3H)-one:

6,8-Dibromobenzoxazinone[8] (3.19 g; 0.01 mole) was treated with hydrazine hydrate (0.75 g; 100%; 0.015 mole) in alcohol (25 ml) and refluxed on steam-bath for 2 hr, cooled and filtered. The solid (2.89 g; 75%) thus obtained was recrystallized from dioxan to get colourless crystals. m p. 238°. [Found: C, 32.38; N, 12.57; $C_9H_7N_3OBr_2$ requires C, 32.43; N, 12.61]. IR: 3320–3290 ($-NH_2$); 1670 (OC–N) and 1600 cm^{-1} (C=N) MS: M^+ 331.

3-Chloroacetamido-6,8-dibromo-2-methyl-quinazolin-4(3H)-one:

3-Aminoquinazolinone (3.33 g; 0.01 mole) and chloroacetyl chloride (1.34 g; 0.012 mole) were refluxed in dry benzene (30 ml) for 3 hr on steam-bath. Benzene was distilled off and the product formed was washed first with 5% sodium bicarbonate solution and then thoroughly with cold water. It was purified by recrystallization from acetic acid to get the colourless crystalline compound (3.27 g; 80%) m.p. 190–92°. [Found: C, 32.22; N, 10.21; $C_{11}H_8N_3O_2ClBr_2$ requires, C, 32.27; N, 10.26]. IR: 3310(–NH), 1730(–NH–CO), 1670(–OC–N–) and 1610 (C=N) cm^{-1}; PMR: δ2.65 (s, 3H,–CH_3), 4.40(s, 2H,–CO–CH_2), 8.15–8.30 (m, 2H, Ar–H) and 9.6–9.8 (b, 1H, –NH–CO); MS: M^+ 407.

N^4[N-(6,8-Dibromo-2-methyl-3-quinazolin-4(3H)-onyl)acetamido]-N^1-substituted sulphanilamides.

To a mixture of 3-chloroacetamido-6,8-dibromo-2-methyl-quinazolin-4(3H)-one (4.0 g; 0.01 mole) and sulphanilamide (1.72 g; 0.01 mole) in alcohol (30 ml), few drops of pyridine were added and refluxed on a steam-bath for 3 hr. Alcohol was distilled off and the residue was poured onto a little crushed ice with stirring. It was kept aside for few minutes and the resulting product was filtered, washed with cold water and recrystallized from aqueous alcohol to get light yellow crystals (3.54 g; 65%). m.p. 118° [Found: C,

37.38; H, 2.69; N, 12.78; $C_{17}H_{15}N_5O_4SBr_2$ requires C, 37.43; H, 2.75; N, 12.84%]. IR: 3140–3180; 3380–3500 (sulphonamide –NH and –NH–CO); 1700 (NH–CO); 1680(–OC–N–); 1610(C=N); 1340 and 1150 cm^{-1} (sulphonamide-SO_2). MS: m/z 358(10%), 331(15%), 316(5%), 273(5%), 246(6%), 232(4%), 185(100%) and 170(40%).

Other members of the series are synthesized similarly and presented in table 1.

Biological Studies:

These were carried out with albino mice weighing (15–20 g) and rats (80–100 g) of either sex. The test compounds and the standard drugs (aspirin and phenylbutazone) were administered at a dose 100 mg/kg i.p. in aqueous suspension of gum accacia.

Toxicity:

ALD_{50} values were determined[9] employing albino mice as test animals.

Analgesic and Anti-inflammatory Activities:

The analgesic acitivity was determined by three standard methods *viz* the tail clip[11] (mechanical), hot plate[12] and writhing[13] method. The percentage protection was calculated and presented in table 1. The anti-inflammatory activity of the compounds was determined by plethysmographic method, which was based on the method of Winter *et al*[14]. Carrageenin was employed for producing oedema. The percentage inhibition of oedema of the present compounds was calculated and presented in table 1.

Antibacterial Activity:

This was determined following Vincent and Vincent filter paper disc method[10]. The bacteria used were *Bacillus megaterium, Bacillus pumilus; Escherichia coli* and *Pseudomonas ovalis.*

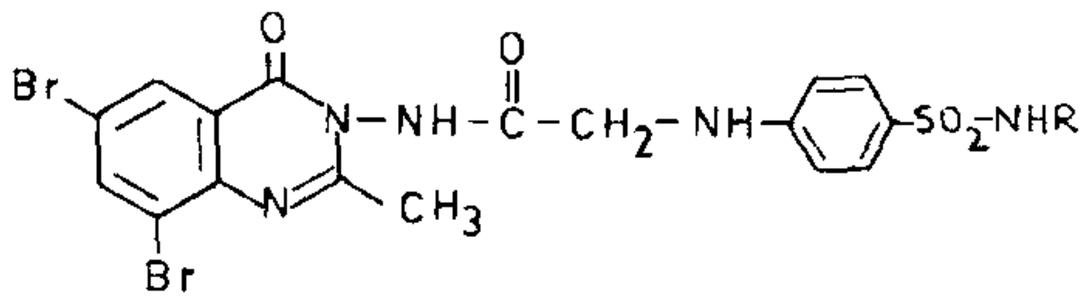
RESULTS AND DISCUSSION

The toxicity studies of the present compounds revealed that they are quite safe, as they failed to produce any toxic symptoms in the test animals even at the dose of 750 μg/kg body weight.

Among the eight compounds screened for analgesic activity, compound 3, followed by 7 was found to be almost on par with aspirin in its analgesic activity, while compound 1 was moderate in its activity. Except compound 4, which showed a weak analgesic activity, all other compounds of the series failed to exhibit any protection.

The results on anti-inflammatory activity of the

Table 1 *Physical Constants, Analgesic and Anti-inflammatory Activities of N^4[N-(6,8-Dibromo-2-methyl-3-quinazolin-4(3H)-onyl)acetamido]N^1-Substituted Sulphanilamides.*



R	m.p. (°C)	Percentage of Nitrogen Obs.	Percentage of Nitrogen Calc.	Mean analgesic activity (percentage protection)	Anti-inflammatory activity (percentage protection rat paw oedema
Hydrogen	118	12.78	12.84	38	53.7
Acetyl	114–16	11.88	11.92	NP	67.5
5-Methoxyisoxazolyl	128	13.38	13.41	66	35.2
5-Methyl-2-(1,3,4-thiadiazolyl)	124	15.19	15.24	15	58.3
1-Phenyl-pyrazolyl	108	14.22	14.26	NP	44.4
4,6-Dimethyl-2-pyrimidyl	121	14.99	15.05	NP	NP
2,6-Dimethyl-4-pyrimidyl	123	14.98	15.05	59	67.5
2,6-Dimethoxy-4-pyrimidyl	112	14.28	14.34	NP	39.8
Aspirin	—	—	—	64	62.0
Phenylbutazone	—	—	—	—	58.0

NP = No Protection

present compounds indicate that compounds 2 and 7 were quite potent in their action which was found to be superior over aspirin, while the activity of the compound 4 followed by 1 was of the order of phenylbutazone. Except compound 6, the other compounds of the series could exhibit a moderate anti-inflammatory activity.

However, the title compounds failed to exhibit any significant bactericidal activity. This may be due to N^4-amino group blocking of the sulphonamides.

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NEWS

YOUNG SCIENTISTS CHOOSING INDUSTRY OVER COLLEGE CAREERS

. . . "A growing number of young scientists are finding industry a friendly place these days to do long range basic research. In the 1970s there was a shift at many companies to more applied research that would produce quick bottom-line results. But lately the pendulum has been swinging back at some companies towards a better balance between basic and applied science. . . . Exxon Corp. estimates that about 15% of the $750 million research and development budget this year is ear-marked for fundamental study in such areas as laser science and surface chemistry. DuPont will spend nearly 20% of its $1 billion research and development budget for 1984 on what it considers basic research, up from only about 10% five years ago. . . . William Phillips, a former Du Pont scientist who now heads the chemistry department at Washington University, in St Louis, says he gets more competition nowadays from companies when he tries to woo top Ph.Ds for assistant professor posts. The American Chemical Society says that on average last year, Ph.D. chemists in industry earned $47,000, while their counterparts at universities made $33,000 and Phillips says there is usually much more money in industry for laboratory equipment and computers. Company scientists also feel less pressure to publish frequently because they aren't preoccupied with academic tenure. (Reproduced with permission from *Press Digest, Current Contents*® No. 35, August 27, 1984, p. 10, Copyright by the Institute for Scientific Information® , Philadelphia, PA, USA).