The release rate constants measured by Samuelov *et al.* (3) also are shown.

The release rate constants for salicylic acid in polyethylene glycol–ethylcellulose and pure ethylcellulose films are shown in Tables I and II. The density of the salicylic acid was taken as 1.443 g/cm^3, and the normalized permeation rate, D_pC_p, of salicylic acid in the polymer was calculated from the lowest solute loading (55 mg/ml) and used in all subsequent computations. The agreement between the release rate constants determined experimentally and those calculated from the model is good.

Similarly, the release rate constants for tripelennamine in polyethylene glycol–ethylcellulose and pure ethylcellulose films are presented in Tables III and IV. The normalized permeation rate of tripelennamine in the polymer was calculated from the lowest solute loading (55 mg/ml), and the density of the dispersed solute was taken as 1.35 g/cm^3. The agreement between theory and experiment again is good.

Friedman *et al.* (9) prepared timed-release dosage forms using ethylcellulose as the polymeric matrix and salicylic acid and caffeine as model drugs. They determined drug release rates for different initial drug concentrations, and their experimental results are presented in Tables V and VI. The values of the release rate constant, K', computed using Eq. 22 also are shown. The diffusivity in the polymer of caffeine and salicylic acid was 2.26×10^{-11} and 1.96×10^{-11} cm^2/sec, respectively. The agreement between the release rate constants determined experimentally and those calculated from the model is good.

There is a good correlation between the model predictions and the measured release rate constants for the drugs. The deviation at very high drug loadings (>30%) can be attributed to interparticle contact. The interparticle contact leads to the formation of channels in the membrane through which the drug can be leached. Therefore, a model of a porous network must be applied. However, up to this limit, the release of drug can be predicted simply from a knowledge of drug loading, drug density, and the permeation rate of the drug in the pure polymers (very low loadings). Comparison of Tables I and II or Tables III and IV shows that plasticized films (with polyethylene glycol) have significantly higher release rate constants than do pure ethylcellulose films. Thus, the diffusivity and solubility of the drug are altered by the addition of plasticizers. The theory could be suitably modified to predict the release rate based on flux enhancer content and will be the subject of a subsequent communication.

Clearly, many properties of the polymer matrix can influence the permeation of drug including the geometry of the dispersed phase (shape, size, and size distribution), the composition of the dispersed phase, and interactions between the phases. However, the simplified model proposed here apparently gives a good correlation to experimental evidence.

REFERENCES

(1) R. W. Baker and H. K. Lonsdale, "Controlled Release of Biologically Active Agents," A. C. Tanquary and K. E. Lacy, Eds., Plenum, New York, N.Y., 1974, p. 21.

(2) T. Higuchi, *J. Pharm. Sci.*, **50**, 874 (1961).

(3) Y. Samuelov, M. Donbrow, and M. Friedman, *ibid.*, **68**, 325 (1979).

(4) H. Fessi, J. P. Marty, F. Puiseux, and J. T. Carstensen, *Int. J. Pharm.*, **1**, 265 (1978).

(5) B. K. Davis, *Proc. Natl. Acad. Sci. USA*, **71**, 3120 (1974).

(6) A. G. Ogsten, *Trans. Faraday Soc.*, **54**, 1754 (1958).

(7) C. Maxwell, "Treatise of Electricity and Magnetism," vol. 1, Oxford University Press, London, England, 1882, p. 365.

(8) R. L. Hamilton and O. K. Crosser, *I & EC Fundam.*, **1**, 189 (1962).

(9) M. Friedman, M. Donbrow, and Y. Samuelov, *J. Pharm. Pharmacol.*, **31**, 396 (1979).

Synthesis and Evaluation of Substituted Quinazolone Derivatives for Antibacterial, Antifungal, and Antiacetylcholinesterase Activities

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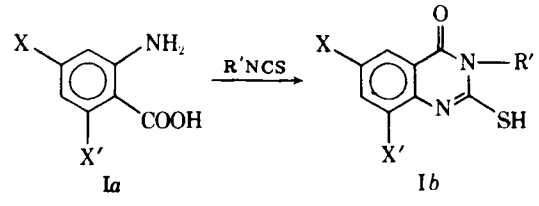
Abstract □ The synthesis of new 6-bromo- and 6,8-dibromo-2-[*N*-(2′-alkyl-1′,3′,4′-thiadiazol-5′-yl)carbamoylmethylthio]-3-aryl/cyclohexyl-4-(3*H*)-quinazolones is described. The synthesized derivatives were screened for antibacterial, antifungal, and antiacetylcholinesterase activities *in vitro*. Most of the compounds exhibited significant biological activity. The relation between their biological activity and chemical structure was studied.

Keyphrases □ Quinazolones—substituted derivatives, synthesis and evaluation for antibacterial, antifungal, and antiacetylcholinesterase activities □ Antibacterial activity—evaluation of substituted quinazolone derivatives □ Antifungal activity—evaluation of substituted quinazolone derivatives □ Antiacetylcholinesterase activity—evaluation of substituted quinazolone derivatives

Various quinazolone derivatives were investigated recently for biological and pharmacological activities such as antibacterial (1–4), antifungal (5, 6), antitubercular (7), antiamoebic (8), antiviral (9), anti-inflammatory (10), anticonvulsant (11, 12), hypotensive (13), and sedative (14, 15) activities. Parmar and coworkers (16, 17) reported the antiacetylcholinesterase activity of quinazolone derivatives.

Since the 1,3,4-thiadiazole nucleus already is well known for its biological activity (18–20), it was decided to combine different 5-chloroacetylamino-2-alkyl-1,3,4-thiadiazole



Ia Ib

X = Br, X′ = H
X = X′ = Br

Scheme I

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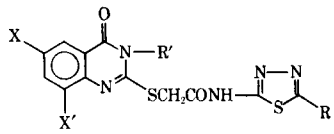


Table I—Physical Constants of Substituted Quinazolone Derivatives

Compound	X	X′	R′	R	Melting Point	Yield, %	Molecular Formula	Nitrogen Analysis, % Calc.	Found
II	Br	H	Benzyl	CH_3	206°	79	$C_{20}H_{16}BrN_5O_2S_2$	13.94	13.71
III	Br	H	Benzyl	C_2H_5	218°	76	$C_{21}H_{18}BrN_5O_2S_2$	13.56	13.37
IV	Br	H	Benzyl	C_3H_7	250°	67	$C_{22}H_{20}BrN_5O_2S_2$	13.20	13.10
V	Br	H	2-Ethylphenyl	CH_3	274°	63	$C_{21}H_{18}BrN_5O_2S_2$	13.56	13.40
VI	Br	H	2-Ethylphenyl	C_2H_5	190°	59	$C_{22}H_{20}BrN_5O_2S_2$	13.20	13.18
VII	Br	H	2-Ethylphenyl	C_3H_7	171°	60	$C_{23}H_{22}BrN_5O_2S_2$	12.86	12.75
VIII	Br	H	Cyclohexyl	CH_3	259°	71	$C_{19}H_{20}BrN_5O_2S_2$	14.17	14.13
IX	Br	H	Cyclohexyl	C_2H_5	258°	67	$C_{20}H_{22}BrN_5O_2S_2$	13.77	13.70
X	Br	H	Cyclohexyl	C_3H_7	228°	69	$C_{21}H_{24}BrN_5O_2S_2$	13.41	13.40
XI	Br	H	4-Methoxyphenyl	CH_3	318°	59	$C_{20}H_{16}BrN_5O_3S_2$	13.51	13.71
XII	Br	H	4-Methoxyphenyl	C_2H_5	324°	57	$C_{21}H_{18}BrN_5O_3S_2$	13.13	13.50
XIII	Br	H	4-Methoxyphenyl	C_3H_7	310°	53	$C_{22}H_{20}BrN_5O_3S_2$	12.82	12.80
XIV	Br	Br	Benzyl	CH_3	220°	76	$C_{20}H_{15}Br_2N_5O_2S_2$	12.05	12.00
XV	Br	Br	Benzyl	C_2H_5	225°	79	$C_{21}H_{17}Br_2N_5O_2S_2$	11.76	11.43
XVI	Br	Br	Benzyl	C_3H_7	218°	71	$C_{22}H_{19}Br_2N_5O_2S_2$	11.49	11.57
XVII	Br	Br	2-Ethylphenyl	CH_3	237°	76	$C_{21}H_{17}Br_2N_5O_2S_2$	11.76	11.75
XVIII	Br	Br	2-Ethylphenyl	C_2H_5	239°	67	$C_{22}H_{19}Br_2N_5O_2S_2$	11.49	11.40
XIX	Br	Br	2-Ethylphenyl	C_3H_7	240°	61	$C_{23}H_{21}Br_2N_5O_2S_2$	11.23	11.20
XX	Br	Br	Cyclohexyl	CH_3	230°	59	$C_{19}H_{19}Br_2N_5O_2S_2$	11.20	11.37
XXI	Br	Br	Cyclohexyl	C_2H_5	240°	55	$C_{20}H_{21}Br_2N_5O_2S_2$	11.92	11.99
XXII	Br	Br	Cyclohexyl	C_3H_7	238°	50	$C_{21}H_{23}Br_2N_5O_2S_2$	11.48	11.50
XXIII	Br	Br	4-Methoxyphenyl	CH_3	232°	61	$C_{20}H_{15}Br_2N_5O_3S_2$	11.72	11.80
XIV	Br	Br	4-Methoxyphenyl	C_2H_5	235°	67	$C_{21}H_{17}Br_2N_5O_3S_2$	11.45	11.21
XV	Br	Br	4-Methoxyphenyl	C_3H_7	231°	59	$C_{22}H_{19}Br_2N_5O_3S_2$	11.20	11.03

Table II—Antiacetylcholinesterase Activity of Substituted Quinazoline Derivatives[a]

Compound	Inhibition at 6.6×10^{-5} M, %	I_{50}[b], $M \times 10^{-5}$
II	5.89	56.0
III	21.06	15.6
IV	25.0	13.2
VIII	15.79	20.8
IX	15.79	20.8
XII	26.32	12.5
XIII	15.79	20.8
XV	21.06	15.6
XVII	26.32	12.5
XVIII	36.843	8.95
XIX	15.80	20.8
XXII	21.06	15.6
XXIV	31.58	10.4
XXV	26.32	12.5

[a] The I_{50} value for neostigmine, a potent acetylcholinesterase inhibitor, used as a standard under similar conditions was 1.96×10^{-7} M. [b] The I_{50} values indicate the molar concentration at which there was 50% inhibition.

Table III—Antibacterial Activity of Substituted Quinazolones

Compound	Average Size of Zone of Inhibition, mm *Staph. aureus*	*B. pumilus*	*B. subtilis*	*Sar. lutea*	*Sal. typhi* H091	*M. tuberculosis*
II	15	7	8	9	11	13
III	9	8	9	13	15	10
IV	—[a]	—[a]	7	10	7	8
V	—[a]	7	—[a]	7	8	—[a]
VI	7	—[a]	8	8	8	—[a]
VII	7	8	—[a]	9	—[a]	7
VIII	7	10	9	7	—[a]	—[a]
IX	—[a]	9	13	12	9	11
X	7	8	13	10	—[a]	7
XI	13	19	17	15	13	18
XII	11	10	9	7	—[a]	13
XIII	10	7	13	9	8	10
XIV	9	13	9	15	17	13
XV	13	15	19	18	9	7
XVI	15	20	17	13	17	14
XVII	7	8	—[a]	7	—[a]	9
XVIII	—[a]	9	15	9	8	—[a]
XIX	10	11	7	8	10	9
XX	7	10	14	7	9	13
XXI	7	9	13	10	12	7
XXII	—[a]	—[a]	7	8	10	—[a]
XXIII	19	15	19	13	17	19
XXIV	15	20	21	17	10	13
XXV	17	10	13	7	13	15
Chloramphenicol[b]	18	17	16	19	17	17
Tetracycline[b]	20	15	16	21	18	15

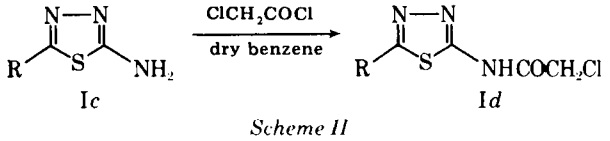
[a] —, compound inactive. [b] Used as a control in the antibacterial screening.

derivatives with the quinazolone nucleus and to study the biological activities of the quinazolone derivatives in continuation of previous work (21–23).

The present report describes the synthesis, characterization, and *in vitro* antibacterial, antifungal, and antiacetylcholinesterase activities of these quinazolone derivatives (II) (Schemes I–III).

EXPERIMENTAL[1]

Chemistry—Several 6-bromo- and 6,8-dibromo-2-mercapto-3-aryl/cyclohexyl-4-(3*H*)-quinazolones (Ib) were synthesized by condensation of 5-bromo- and 3,5-dibromo-2-aminobenzoic acids (Ia) with different substituted aryl isothiocyanates in ethanol. With the method of Gagiu and Mavrodin (24), different 5-chloroacetylamino-2-alkyl-1,3,4-thiadiazole derivatives (Id) were obtained in good yield by refluxing 2-alkyl-5-amino-1,3,4-thiadiazoles (Ic) in dry benzene with chloroacetyl chloride. The intermediate 2-alkyl-5-amino-1,3,4-thiadiazoles were prepared by a literature method (25). When the 2-mercapto-3-aryl/cyclohexyl-4-



Ic Id

Scheme II

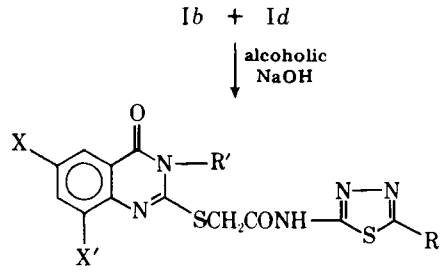
[1] All compounds were analyzed for their nitrogen content. Melting points were taken in open capillary tubes with a partial immersion thermometer and are corrected. IR spectra were obtained with a Perkin-Elmer model 137 Infracord spectrophotometer, equipped with sodium chloride optics, in potassium bromide films in the 700–3500-cm^{-1} range.

Table IV—Antifungal Activity of Substituted Quinazolones [a]

Compound	Concentrations	Average Inhibition after 1 Week, %					
		A. niger	*M. canis*	*A. fumigatus*	*F. moniliforme*	*P. nonatum*	*R. stolonifer*
II	1:1000	41.6	56.7	51.7	38.5	49.3	58.3
	1:10,000	33.3	51.3	47.3	35.3	42.3	47.3
	1:100,000	20.0	42.3	40.0	32.7	39.7	35.2
III	1:1000	58.5	51.4	56.7	67.3	43.7	35.5
	1:10,000	47.3	42.3	45.3	56.4	45.6	28.0
	1:100,000	32.3	37.4	40.1	40.7	47.6	25.3
IV	1:1000	51.3	54.7	47.3	43.7	25.3	27.3
	1:10,000	45.3	50.3	45.3	38.7	19.3	21.3
	1:100,000	47.9	45.5	40.1	25.3	15.4	20.3
V	1:1000	45.5	37.5	55.5	45.6	41.4	35.5
	1:10,000	41.3	33.4	45.6	41.6	40.0	32.3
	1:100,000	37.5	30.0	40.0	37.3	38.0	27.3
VI	1:1000	76.3	67.3	67.3	56.7	87.3	67.9
	1:10,000	45.3	56.4	47.4	53.3	79.5	63.7
	1:100,000	35.7	41.4	40.0	51.2	70.3	60.4
VII	1:1000	81.3	74.4	67.4	45.5	42.7	47.3
	1:10,000	73.7	70.5	60.4	40.1	40.1	45.2
	1:100,000	54.3	61.5	57.5	37.5	37.5	40.3
VIII	1:1000	37.5	25.3	35.5	45.5	36.5	50.0
	1:10,000	30.1	21.5	31.5	40.1	31.3	45.7
	1:100,000	29.1	17.3	27.9	37.5	27.9	41.3
IX	1:1000	47.3	37.3	27.3	25.3	35.6	29.3
	1:10,000	43.2	29.5	25.3	20.4	31.7	25.4
	1:100,000	39.3	25.3	20.9	17.4	28.5	21.4
X	1:1000	37.3	28.3	57.3	47.3	41.5	21.5
	1:10,000	31.4	21.5	45.3	42.1	37.5	20.1
	1:100,000	27.3	17.5	37.4	39.5	30.8	18.3
XI	1:1000	87.3	93.4	81.1	82.1	71.4	47.3
	1:10,000	71.5	87.1	73.3	73.8	67.3	42.1
	1:100,000	69.0	75.6	67.5	56.7	59.7	37.5
XII	1:1000	56.3	67.3	51.5	40.0	51.5	59.0
	1:10,000	47.3	51.8	45.3	37.3	47.5	51.1
	1:100,000	31.5	47.5	41.0	29.0	41.0	49.1
XIII	1:1000	45.0	57.3	43.0	42.0	49.0	47.0
	1:10,000	41.0	51.5	40.0	40.0	41.0	40.0
	1:100,000	40.0	45.7	35.0	33.3	35.5	38.8
XIV	1:1000	97.3	87.3	75.5	85.5	95.5	89.0
	1:10,000	95.4	82.1	71.5	80.0	90.0	85.0
	1:100,000	90.5	76.1	67.9	78.8	85.0	80.0
XV	1:1000	85.6	81.1	70.1	67.3	73.4	70.0
	1:10,000	81.7	80.0	67.1	61.1	70.9	65.5
	1:100,000	75.5	71.0	57.1	56.1	65.9	61.6
XVI	1:1000	51.5	67.3	59.0	61.6	73.1	41.5
	1:10,000	47.7	62.3	57.4	51.1	68.5	39.1
	1:100,000	41.1	51.4	51.5	45.7	56.3	34.5
XVII	1:1000	67.5	56.1	57.1	67.1	49.5	47.1
	1:10,000	63.2	51.1	41.1	61.5	40.0	41.0
	1:100,000	57.1	45.5	34.5	49.0	35.6	37.0
XVIII	1:1000	57.1	45.1	49.0	67.3	61.0	57.5
	1:10,000	40.1	42.1	45.5	61.0	57.3	53.4
	1:100,000	35.3	39.5	40.0	57.3	51.4	50.0
XIX	1:1000	41.5	40.0	41.0	29.0	47.3	40.0
	1:10,000	37.5	35.5	29.0	27.0	41.5	37.9
	1:100,000	30.5	31.6	27.3	21.0	40.1	34.5
XX	1:1000	87.3	76.6	65.5	42.2	67.7	51.0
	1:10,000	81.5	74.0	60.0	41.0	61.1	45.0
	1:100,000	78.1	70.0	57.7	39.1	55.0	42.0
XXI	1:1000	81.1	73.3	69.0	57.0	61.1	63.3
	1:10,000	78.3	71.0	62.0	51.0	59.9	61.0
	1:100,000	70.1	65.0	60.0	45.8	55.5	57.7
XXII	1:1000	67.7	68.0	53.5	41.1	47.7	63.1
	1:10,000	61.1	40.0	40.0	34.4	41.1	57.3
	1:100,000	53.4	37.0	37.3	30.0	35.7	41.1
XXIII	1:1000	89.0	93.7	87.0	81.1	97.0	90.0
	1:10,000	81.0	90.0	81.0	78.1	91.0	85.5
	1:100,000	76.6	85.0	78.0	75.5	87.7	80.0
XXIV	1:1000	78.3	67.3	71.8	84.1	78.1	58.0
	1:10,000	75.1	65.0	65.1	80.0	70.1	51.0
	1:100,000	70.0	60.6	61.1	70.0	59.0	45.5
XXV	1:1000	67.5	57.1	45.0	61.6	45.4	37.3
	1:10,000	61.0	51.0	40.0	59.0	41.4	30.1
	1:100,000	57.7	47.0	37.7	51.5	37.4	28.7

[a] Griseofulvin, a potent fungicide, was used as a control.

(3*H*)-quinazolones were refluxed in alcoholic sodium hydroxide with different 5-chloroacetylamino-2-alkyl-1,3,4-thiadiazoles, 24 new 6-bromo- and 6,8-dibromo-2-[*N*-(2′-alkyl-1′,3′,4′-thiadiazol-5′-yl)carbamoylmethylthio]-3-aryl/cyclohexyl-4-(3*H*)-quinazolones (II) with varying alkyl groups in the thiadiazole nucleus and different aryl functions in the quinazolone nucleus were obtained (Table I).



II

Scheme III

Synthesis—*6-Bromo- and 6,8-Dibromo-2-mercapto-3-aryl/cyclohexyl-4-(3H)-quinazolones (Ib)*—These compounds were prepared by the method described by Bhargava and Lakhan (26).

To a solution of 5-bromo-2-aminobenzoic acid (0.01 mole) in absolute ethanol (50 ml) was added 1.41 g (0.01 mole) of cyclohexylisothiocyanate. The resulting solution was heated under reflux on a steam bath for 5 hr, at which time a crystalline solid mass was obtained. The solid mass was separated by filtration, washed with cold ethanol, and recrystallized from ethanol.

Various other quinazolones (Ib) were prepared in a similar manner.

6-Bromo- and 6,8-Dibromo-2-[N-(2'-alkyl-1',3',4'-thiadiazol-5'-yl)carbamoylmethylthio] -3- aryl/cyclohexyl -4- (3H)-quinazolones (II)—To a solution of sodium hydroxide (0.4 g, 0.1 mole) in 30 ml of 80% ethanol was added 3.47 g (0.01 mole) of 6-bromo-2-mercapto-3-benzyl-4-(3*H*)-quinazolone, and the mixture was stirred until a clear solution was obtained. 5-Chloroacetylamino-2-methyl-1,3,4-thiadiazole (1.92 g, 0.01 mole) was added, and the solution was heated under reflux for 5 hr. After cooling, the reaction mixture was poured into 200 ml of ice-cold water; the solid mass was filtered, washed with cold water, and crystallized from ethanol.

Other quinazolone derivatives (II) were prepared in a similar manner and are listed in Table I.

All of the synthesized quinazolone derivatives (II) (Table I) were characterized by their sharp melting points and elemental analyses. The IR spectra of the final compounds (II) showed the characteristic absorption bands of C=N (~1600 cm^{-1}), CH_2CON (~1680 cm^{-1}), CONH (~1660 cm^{-1}), and C=O (1700 cm^{-1}). Absence of the SH vibration at 2550 cm^{-1} provided further support for their molecular structure. These absorption bands correspond to the characteristic quinazolone bands (27).

Biological Screening—All compounds reported in Table I were assayed *in vitro* for antibacterial activity against six bacteria: *Staphylococcus aureus*[2] (NCTC 7447), *Bacillus pumilus*[2] (NCTC 8241), *Bacillus subtilis*[2] (NCTC 8236), *Sarcina lutea*[2] (ATCC 9341), *Salmonella typhi*[3] H091 (NCTC 3111), and *Mycobacterium tuberculosis*[3] ($H_{37}Rv$). Their antifungal activity was screened against several fungi: *Aspergillus niger*[4] (ATCC 12845), *Microsporum canis*[3] (VM 200-USPHS), *Aspergillus fumigatus*[3] (68LI), *Fusarium moniliforme*[4] (ATCC 10052), *Penicillium nonatum*[4] (ATCC 9179), and *Rhizopus stolonifer*[4] (ATCC 10404).

Of the 24 quinazolone derivatives (Table I), 14 also were tested for their antiacetylcholinesterase activity (Table II).

Determination of Antibacterial Activity—The *in vitro* antibacterial activity was determined by an agar plate diffusion method (28). The agar medium was inoculated with 1 ml of a 24-hr-old culture of the test organism. Filter paper disks (5 mm in diameter) saturated with the test compounds (10 mg/ml in ethanol) were placed on nutrient agar after the ethanol was dried. After incubation for 36 hr, the zones of inhibition around the disks were measured.

All experiments were performed in duplicate, and the results are recorded in Table III.

Determination of Antifungal Activity—The agar plate diffusion technique (29) was employed for the determination of the antifungal activity of the synthesized compounds. Three concentrations (1:1000, 1:10,000, and 1:100,000) were used. One milliliter of each compound was poured into separate petri dishes. Approximately 20–25 ml of molten Czapek-Dox agar medium was added to each petri dish.

All experiments were performed in triplicate. The average percentage inhibition given by the various compounds after 1 week is given in Table IV.

Determination of Antiacetylcholinesterase Activity—Male rats, ~150–200 g, were decapitated, and the brains were removed quickly, weighed, and homogenized in a glass homogenizer[5] using a polytef pestle. A 1% (w/v) homogenate in phosphate saline was used without further purification as the enzyme source.

The enzyme activity was assayed essentially according to the method proposed by Diggle and Gage (30), which is a modification of Hestrin's (31) method. The 2.7-ml assay system contained 0.5 ml of phosphate saline, 1.0 ml of acetylcholine bromide solution, 0.2 ml of inhibitor solution in propylene glycol, and 1.0 ml of the enzyme source. The enzyme was kept with the inhibitor at 37° for 5 min. The reaction was started with the addition of acetylcholine (only in experimental tubes).

The tubes were kept at 37° for 15 min, after which the reaction was stopped by the addition of 2.0 ml of alkaline hydroxylamine hydrochloride. Thereafter, 1.0 ml of acetylcholine solution was added to the control tubes. Then 1.0 ml of diluted hydrochloric acid was added to all of the tubes, followed by the addition of 1.5 ml of ferric chloride solution and water to bring the volume to 7.5 ml in each tube. The absorbance was recorded in a spectrophotometer[6] at 540 nm. The inhibition obtained was recorded in Table II along with the I_{50} values of the quinazolone derivatives, which indicate the concentration required to produce 50% enzyme inhibition.

RESULTS AND DISCUSSION

The results shown in Table III indicate that all of the compounds exhibited antibacterial activity against at least one type of bacteria. In comparison to the 6-bromo quinazolone derivatives (II–XIII), 6,8-dibromo quinazolone derivatives (XIV–XXV) were more effective antibacterial compounds. When the benzyl or 4-methoxyphenyl group was substituted at the 3-position in the quinazolone nucleus, the activity increased (II–IV, XI–XVI, and XXIII–XXV). 2-Ethylphenyl-substituted quinazolone derivatives (V–VII and XVII–XIX) exhibited comparatively poor antibacterial activity. All compounds exhibited increased antibacterial activity against *S. lutea* (ATCC 9341). Compounds XI, XVI, and XXIII exhibited good antibacterial activity.

From the toxicity data given in Table IV, it is evident that all of the compounds possess variable antifungal activity against the fungi tested. The 6,8-dibromo quinazolone derivatives were more effective antifungal agents than the 6-bromo quinazolone derivatives. Substitution of the benzyl group at the 3-position of the quinazolone nucleus led to II–IV and XIV–XVI, which were more effective antifungal compounds. Furthermore, the electron-donating group 2-ethylphenyl decreased the fungitoxicity of the test compounds while the electron-withdrawing group 4-methoxyphenyl increased the fungitoxicity. Cyclohexyl substitution at the 3-position of the quinazolone nucleus rendered VIII–X and XX–XXII less fungitoxic against the fungi tested.Compounds XI and XXIII were better antifungal agents.

The results of the antiacetylcholinesterase test *in vitro* against 14 synthesized quinazolone derivatives are recorded in Table II. The screening data indicate that all of these derivatives exhibited marginal activity. Compounds XVIII and XXIV were more active, while II was inactive. Furthermore, 6,8-dibromo-substituted quinazolone derivatives were more potent in comparison to 6-bromo-substituted derivatives. Compounds III, XV, and XXII exhibited equal I_{50} values, as did XII, XVII, and XXV and also VIII, IX, and XIII.

REFERENCES

(1) P. N. Bhargava and M. R. Chaurasia, *J. Indian Chem. Soc.*, **53**, 46 (1976).

(2) S. K. V. Seshavataram and N. V. Subba Rao, *Proc. Indian Acad. Sci., Sec. A*, **85**, 81 (1977).

(3) R. S. Verma, *J. Indian Chem. Soc.*, **52**, 344 (1975).

(4) J. Klosa, German pat. 1,200,307 (1965); through *Chem. Abstr.*, **63**, 18113e (1965).

(5) P. C. Joshi and P. C. Joshi, *J. Indian Chem. Soc.*, **55**, 465 (1978).

(6) N. Home and H. Reinshagen, German pat. 2,619,110 (1976); through *Chem. Abstr.*, **88**, 72696e (1977).

(7) M. K. Jain and K. S. Narang, *J. Indian Chem. Soc.*, **30**, 711

[2] Obtained from Public Analyst Department, U.P. Government, Lucknow, India.

[3] Obtained from Central Drug Research Institute, Lucknow, India.

[4] Obtained from Cane Sugar Research Institute, Lucknow, India.

[5] Potter Elvehjem type A.

[6] Spectrochem.

(1953).
(8) A. B. Sen and S. K. Gupta, *ibid.*, **39**, 369 (1962).
(9) B. M. Gupta, S. K. Khan, and U. Agarwal, *J. Sci. Ind. Res.*, **21**, 189 (1962).
(10) M. Seth and N. M. Khanna, *Indian J. Chem.*, **14**, 536 (1976).
(11) M. L. Gujral, K. N. Sareen, and R. P. Kohli, *Indian J. Med. Res.*, **45**, 207 (1957).
(12) K. C. Joshi, V. K. Singh, D. S. Mehta, R. C. Sharma, and L. Gupta, *J. Pharm. Sci.*, **64**, 1428 (1975).
(13) H. C. Scarborough, U.S. pat. 3,073,826 (1963).
(14) B. Camillo and A. David, *J. Pharm. Pharmacol.*, **12**, 501 (1960).
(15) G. B. Jackman, V. Petrov, and O. Stephensen, *ibid.*, **12**, 529 (1960).
(16) S. S. Parmar, L. D. Joshi, K. Kishore, and R. Kumar, *Biochem. Pharmacol.*, **15**, 723 (1966).
(17) J. P. Barthwal, S. K. Tandon, V. K. Agarwal, K. S. Dixit, and S. S. Parmar, *J. Pharm. Sci.*, **62**, 613 (1973).
(18) H. Kawada, E. Yoshinaga, I. Chiyomaru, and H. Ito, Japanese pat. 7,748,178 (1977); through *Chem. Abstr.*, **88**, 132018p (1978).
(19) L. Nuesslein, E. A. Pieroch, and K. Roeder, U.S. pat. 4,061,645 (1977); through *Chem. Abstr.*, **88**, 62397k (1978).
(20) K. John (Velsicol Chemical Corp.), U.S. pat. 4,052,193 (1977); through *Chem. Abstr.*, **88**, 22929d (1978).
(21) A. K. Sen Gupta and H. K. Misra, *Indian J. Chem.* **17**, 185 (1979).
(22) *Ibid.*, **18**, 381 (1979).
(23) A. K. Sen Gupta and H. K. Misra, *Agr. Biol. Chem., Jpn.*, **44**, 1009 (1980).
(24) F. Gagiu and Al. Mavrodin, *Bull. Soc. Chim. Fr.*, **3**, 1010 (1967).
(25) Japanese pat. 20,944 (1966); through *Chem. Abstr.*, **66**, 46430f (1967).
(26) P. N. Bhargava and R. Lakhan, *Curr. Sci.*, **36**, 575 (1967).
(27) H. Culbertoson, J. C. Decius, and B. E. Christensen, *J. Am. Chem. Soc.*, **74**, 4834 (1952).
(28) R. S. Varma, S. A. Imam, and W. L. Nobles, *J. Pharm. Sci.*, **62**, 140 (1973).
(29) J. G. Horshfall, *Bot. Rev.*, **5**, 357 (1945).
(30) W. M. Diggle and J. G. Gage, *Biochem. J.*, **49**, 491 (1951).
(31) S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).

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Comparison of Polyethylene Glycol and Polyoxyethylene Stearate as Excipients for Solid Dispersion Systems of Griseofulvin and Tolbutamide I: Phase Equilibria

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Abstract □ Phase equilibrium diagrams were constructed based on hot-stage microscopy and differential scanning calorimetry of solid dispersions of griseofulvin or tolbutamide in polyethylene glycol 2000 or polyoxyethylene 40 stearate. The solid dispersions were prepared by physical mixing, fusion, and coprecipitation from ethanol. The phase diagrams were largely independent of the method of preparation of the dispersion systems. The diagrams were of the monotectic type for polyethylene glycol 2000 with each drug and for griseofulvin with each excipient, with the monotectic species being the pure drug. Polyoxyethylene 40 stearate with tolbutamide gave eutectic systems in which liquid polyoxyethylene 40 stearate dissolved up to 20% of the tolbutamide. The phase diagrams showed greater solubility of tolbutamide in liquid polyoxyethylene 40 stearate than in polyethylene glycol 2000 but showed a similar solubility of griseofulvin in each excipient. Solid solution formation was not detected.

Keyphrases □ Excipients—polyethylene glycol and polyoxyethylene stearate, comparison as excipients for solid dispersion systems of griseofulvin and tolbutamide, phase equilibria □ Polyethylene glycol—comparison with polyoxyethylene stearate as excipient for solid dispersion systems of griseofulvin and tolbutamide, phase equilibria □ Polyoxyethylene stearate—comparison with polyethylene glycol as excipient for solid dispersion systems of griseofulvin and tolbutamide, phase equilibria

The use of a eutectic mixture containing a water-soluble compound to increase the dissolution rate and bioavailability of a sparingly soluble drug first was demonstrated by Sekiguchi and Obi (1). As the water-soluble matrix dissolves, the insoluble drug is exposed to the dissolution medium in a very fine state of subdivision. This type of formulation, a solid dispersion system, has been investigated extensively and has been extended to include solid solutions of drug in water-soluble excipients (2). Solid solutions should offer greater increases in the dissolution rate and bioavailability than eutectic mixtures, because the drug is dispersed as single molecules in solid solutions but as solid microscopic particles in the latter case.

BACKGROUND

Solid dispersions of griseofulvin in polyethylene glycols of high molecular weight (3, 4) have excited much interest. The dissolution rate and bioavailability of griseofulvin from such solid dispersions clearly are greater than those of the micronized or microcrystalline drug (5). These phenomena previously were attributed to the formation of solid solutions, but Chiou (6) recently showed that griseofulvin has negligible or very limited solid solubility in polyethylene glycol dispersion systems. The marked enhancement of the dissolution and absorption rates of griseo-

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