Synthesis and biological activity of some new 4-thiazolidinone derivatives

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4-Thiazolidinone is a medicinally important moiety. We have used thiourea with other potential moiety 4-quinazolinone to enhance medicinal value of the 4-thiazolidinones moiety. 15 new compounds are reported along with their spectral data, antibacterial and antitubercular activities.

4-Thiazolidinones have been found to be endowed with a variety of biological activities¹⁻⁵. Keeping in view the medicinal importance and utility of thiazolidine moiety, it was worth attempting to synthesize some new potential 4-oxothiazolidines in which the side chain of actithiazic acid in position-2 is shifted to position-5 in 4-thiazolidinone with substituting other groups in the ring. In the present paper, we have incorporated well-known organic synthon thiourea with another potential moiety 4-quinazolinone to augment medicinal value of the compounds. All the new compounds were screened for their antibacterial and antitubercular activities.

Results and discussion

Biological activity :

The compounds were screened for antibacterial activity using cup-plate method⁶. The testing was carried out in DMF solution at a concentration of 50 $\mu\text{g ml}^{-1}$ using gram positive bacteria like *Staphylococcus aureus* and gram negative bacteria like *Escherichia coli* and *Salmonella typhosa*. Chloramphenicol was used as a standard drug.

Antitubercular activity of the synthesized compounds :

This activity was carried out at TAACF (Tuberculosis Antimicrobial Acquisition and Coordinating Facility), Southern Research Institute, Birmingham, Alabama. The following procedure was used. The TAACF integrates the various components of the drug discovery and development process into a unified program that facilitates the search for antimycobacterial drugs. This program consists of four closely interwoven components; a compound acquisition, repository, and data analysis service operated by Southern Research Institute; an *in vitro* screening service at the GWL Hansen's Disease Center; and *in vivo* screening service at Colorado State University; and a technology transfer service at Research Triangle Institute.

where, Ar = different aryl groups cited in Table 1.

Under the direction of the U.S. National Institute of Allergy and Infectious Diseases (NIAID), Southern Research Institute coordinates the overall program. All services are provided confidentially and at no cost to the supplier.

In vitro evaluation of antimycobacterial activity :

Primary screening conducted at 12.50 $\mu\text{g ml}^{-1}$ (or molar equivalent of highest molecular weight compound in a series of congeners) against *Mycobacterium tuberculosis* H₃₇R_v (ATCC 27294) in BACTEC 12B medium using a broth microdilution assay, the Microplate Alamar

Table 1. Physical data for the synthesized compounds*

Compd.	Sample ID	Ar	Molecular formula	Yield %	M.p. °C
4a	125312	C ₆ H ₅	C ₂₄ H ₁₇ N ₃ O ₂ S ₂	71.20	121
b	125313	2(OH)C ₆ H ₄	C ₂₄ H ₁₇ N ₃ O ₃ S ₂	67.00	137
c	125314	3(OH)C ₆ H ₄	C ₂₄ H ₁₇ N ₃ O ₃ S ₂	69.40	183
d	125315	4(OH)C ₆ H ₄	C ₂₄ H ₁₇ N ₃ O ₃ S ₂	70.30	133
e	125316	4(Cl)C ₆ H ₄	C ₂₄ H ₁₆ N ₃ O ₂ S ₂ Cl	68.00	175
f	125317	4(OCH ₃)C ₆ H ₄	C ₂₅ H ₁₉ N ₃ O ₃ S ₂	71.60	104
g	125318	3,4,5(OCH ₃) ₃ C ₆ H ₂	C ₂₇ H ₂₃ N ₃ O ₅ S ₂	69.00	111
h	125319	2(Cl)C ₆ H ₄	C ₂₄ H ₁₆ N ₃ O ₂ S ₂ Cl	67.80	163
i	125320	3,4(Cl) ₂ C ₆ H ₃	C ₂₄ H ₁₅ N ₃ O ₂ S ₂ Cl ₂	70.00	125
j	125321	3(NO ₂)C ₆ H ₄	C ₂₄ H ₁₆ N ₄ O ₄ S ₂	65.00	97
k	125322	4(CH ₃)C ₆ H ₄	C ₂₅ H ₁₉ N ₃ O ₂ S ₂	65.90	119
l	125323	-CH=CH-C ₆ H ₅	C ₂₆ H ₁₉ N ₃ O ₂ S ₂	71.00	91
m	125324	3,4-O-CH ₂ -O-C ₆ H ₃	C ₂₅ H ₁₇ N ₃ O ₄ S ₂	69.40	157
n	125325	3(OCH ₃)4(OH)C ₆ H ₃	C ₂₅ H ₁₉ N ₃ O ₄ S ₂	70.50	115
o	125326	2(OH)5(Br)C ₆ H ₃	C ₂₄ H ₁₆ N ₃ O ₃ S ₂ Br	73.70	178

*All compounds gave satisfactory C, H, N and S analyses.

Blue Assay (MABA)⁷. Compounds exhibiting fluorescence are tested in the BACTEC 460 radiometric system. Compounds effecting <90% inhibition in the primary screen (i.e., MIC > 12.50 µg ml⁻¹) are not generally evaluated further.

Minimum compound requirements : 1.0 mg.

Conclusion :

Most of the compounds were found moderately active (14–26 mm zone of inhibition). Comparatively significant activity was observed in compound bearing substituents 2-hydroxy-5-bromophenyl (24), 4-hydroxyphenyl (20), 2-chlorophenyl (22), 4-chlorophenyl (24), 4-methoxyphenyl (26) and 3-nitrophenyl (20 mm). None of the synthesized compounds was found active at 12.50 µg ml⁻¹ concentration against *Mycobacterium tuberculosis* H₃₇R_v.

Experimental

All melting points were taken in open capillaries and are uncorrected. The structures of the new products were confirmed by the elemental and spectral analysis. IR spectra (KBr) were recorded on a Shimadzu FTIR spectrophotometer, ¹H NMR spectra (CDCl₃ + TFA) on Bruker (200 MHz) and Hitachi 1200 (60 MHz) spectrometers using TMS as internal reference and mass spectra on a Jeol JMSD-300 spectrometer.

Synthesis of 2-phenyl-3-1-benzoxazin-4(4H)-one⁸ (1) :

Benzoyl chloride (140.5 g; 1 M) was added dropwise

to anthranilic acid (137 g; 1 M) dissolved in pyridine (60 ml) with constant stirring at 8° over the period of 1 h. After the completion of addition, the reaction mixture was stirred for half an hour at RT. At the end of the reaction, solid mass was obtained. It was filtered, washed successively with sodium bicarbonate solution (to remove unreacted acid) and then water, dried and recrystallised from rectified spirit. Yield (178.5 g, 80%), m.p. 114° (Found : N, 6.13, C₁₄H₉NO₂ requires : N, 6.27%).

Synthesis of 2-phenyl-3-thiocarboxamide-4-oxoquinazoline⁸ (2) :

2-Phenyl-3,1-benzoxazin-4(4H)-one (111.5 g; 0.5 M) was treated with equimolar proportion of thiourea (38 g; 0.5 M) using ethanol (250 ml) as solvent. The contents were refluxed for 3 h. The excess of solvent was then distilled off, and the resulting solid was dried and recrystallised from rectified spirit. Yield (101.10 g, 72%), m.p. 189° (Found : N, 14.87; S, 11.25. C₁₅H₁₁N₃OS requires N, 14.93; S, 11.38%).

Synthesis of 2-phenyl-3-(2-hydroxybenzaliminothiocarbonyl)-4-oxoquinazoline⁹ (3) :

A mixture of 2-phenyl-3-thiocarboxamido-4-oxoquinazoline (2.81 g; 0.01 M) and salicylaldehyde (1.22 g; 0.01 M) in methanol was refluxed on a water-bath for 3 h. The clear solution was poured in ice-water, filtered the solid and recrystallised from ethanol (95%). Yield (3.11 g, 81%), m.p. 207° (Found : N, 10.85; S, 8.22. C₂₂H₁₅N₃O₂S requires : N, 10.90; S, 8.31%; ν_{max} 3065

(-CH str., aromatic), 1660 ($>C=O$ str., quinazoline), 3415 (-OH phenolic), 1650 (-CH=N-), 1259 ($>C=S$ str.), 1545 cm^{-1} (C=C str., quinazoline) and 1H NMR δ 6.8 (1H, s, -CH=), 7.6–8.2 (m, Ar-H), 8.5 (s, Ar-OH).

Synthesis of 2-(2-hydroxyphenyl)-3-[(2-phenyl-4-oxo-3-quinazolinyl)-thiocarbonyl]-4-oxo-thiazolidine (4) :

To a solution of 2-phenyl-3-(2-hydroxybenzalimino-thiocarbonyl)-4-oxo-quinazoline (1.92 g; 0.005 M) in 1,4-dioxan (25 ml) was added thioglycolic acid (0.464 g; 0.005 M) with stirring. The mixture was refluxed on steam-bath for 8 h, cooled and poured into sodium bicarbonate solution (4 M). The resulting solid was washed with water, dried and recrystallised from rectified spirit. Yield (1.53 g, 67%), m.p. 137° (Found : N, 9.09; S, 13.75. $C_{24}H_{17}N_3O_2S_2$ requires : N, 9.15; S, 13.94%).

Other compounds reported in Table 1 were synthesized following the same procedure.

Spectral data of the synthesized compound (4) :

ν_{max} 3065 (-CH str., aromatic), 1764.5 (C=O str., thiazolidine), 1660 (C=O str., quinazoline), 1620 (C=N str., quinazoline), 1572 (C–N str., thiazolidine), 1525 (C=C str., quinazoline), 685 (C–S–C str., thiazolidine), 1240 ($>C=S$ str.,) 3415 (-OH phenolic), 1433 cm^{-1} (CH deformation of -CH₂CO- group); δ 3.5 (2H, singlet, CH₂S), 5.35 (1H, singlet, CH-Ar), 7.6–8.2 (multiplet, Ar-H), 10.5 (-OH, singlet), 6.14 (1H, thiazolidine).

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