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.

Results and discussion

Biological activity:

The compounds were screened for antibacterial activity using cup-plate method. The testing was carried out in DMF solution at a concentration of 50 μg 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 an in vivo screening service at Colorado State University; and a technology transfer service at Research Triangle Institute.

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 μg ml⁻¹ (or molar equivalent of highest molecular weight compound in a series of congeners) against Mycobacterium tuberculosis H₃⁷Rv (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    | C₆H₅                | C₂₄H₁₇N₁₃O₂S₂    | 71.20   | 121    |
| b      | 125313    | 2(OH)C₆H₄           | C₂₄H₁₇N₁₃O₂S₂    | 67.00   | 137    |
| c      | 125314    | 3(OH)C₆H₄           | C₂₄H₁₇N₁₃O₂S₂    | 69.40   | 183    |
| d      | 125315    | 4(OH)C₆H₄           | C₂₄H₁₇N₁₃O₂S₂    | 70.30   | 133    |
| e      | 125316    | 4(Cl)C₆H₄           | C₂₄H₁₇N₁₃O₂S₂Cl  | 68.00   | 175    |
| f      | 125317    | 4(OCH₃)C₆H₄         | C₂₅H₁₉N₂O₂S₂    | 71.60   | 104    |
| g      | 125318    | 3,4,5(OCH₃)₃C₆H₂   | C₂₅H₁₉N₂O₂S₂    | 69.00   | 111    |
| h      | 125319    | 2(Cl)C₆H₄           | C₂₄H₁₆N₁₃O₂S₂Cl  | 70.00   | 125    |
| i      | 125320    | 3,4(Cl)₂C₆H₄        | C₂₄H₁₆N₁₃O₂S₂Cl  | 65.00   | 97     |
| j      | 125321    | 3(NO₂)C₆H₄          | C₂₅H₁₉N₂O₂S₂    | 65.90   | 119    |
| k      | 125322    | 4(CH₃)C₆H₄          | C₂₅H₁₉N₂O₂S₂    | 71.00   | 91     |
| l      | 125323    | -CH=CH-C₆H₄         | C₂₅H₁₉N₂O₂S₂    | 69.40   | 157    |
| m      | 125324    | 3,4-O-CH₂-O-C₆H₃   | C₂₆H₁₉N₂O₄S₂    | 70.50   | 115    |
| n      | 125325    | 3(OCH₃)₄(OH)C₆H₃   | C₂₆H₁₉N₂O₄S₂    | 73.70   | 178    |
| o      | 125326    | 2(OH)5(Br)C₆H₃     | C₂₆H₁₉N₂O₄S₂Br  | 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 H₃⁷Rₐ.

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, C₁₄H₉N₀₂ requires : N, 6.27%).

Synthesis of 2-phenyl-3-thiocarboxamide-4-oxo-quinazoline⁸ (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. C₁₅H₁₁N₃O₂S 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. C₂₂H₁₅N₅O₂S requires : N, 10.90; S, 8.31%; μₘₙₓ 3065
(-CH str., aromatic), 1660 (>C=O str., quinazoline), 3415 (-OH phenolic), 1650 (>C=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 N). 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. C₂₄H₁₇N₃O₂S₂ requires : N, 9.15; S, 13.94%).

Other compounds reported in Table I 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 (multiplate, Ar-H), 10.5 (-OH, singlet), 6.14 (1H, thiazolidine).

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