Synthesis And Comparison Of Biological Activities Of Azetidinone, Thiazolidinone And Related Compounds

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Abstract

Recent discoveries of non-classical β-lactam antibiotics such as nocardicines, monobactams and thienamycin have stimulated much interest[1,2,3]. Besides this, the unique feature of these strained molecules is that these heterocycles are becoming powerful building blocks for the synthesis of a variety of organic compounds[4,5]. During the present work, azetidinone and thiazolidinone derivatives of 3-chloro, 4-fluoro aniline and 4-chloro aniline were prepared. The synthesis was further extended for deriving arylidene derivatives from the thiazolidinones.

Introduction

Although number of compounds are synthesized year after year and newer antibiotics have been discovered, many disadvantages of chemotherapy particularly the emergence of resistant strains is still a major problem. The general strategy to synthesize new effective drugs is to exploit the lead compounds, which can be from the established drugs. The molecular manipulation of a promising lead compound is a major line of approach to new drugs.

During the present work, azetidinone and thiazolidinone derivatives from 3-chloro, 4-fluoro aniline and 4-chloro aniline were prepared and the synthesis was further extended to arylidene derivatives of the respective thiazolidinones. It is already known that an isosteric replacement in antidepressant like imipramine with an introduction of a carbon-carbon double bond in a cyclic structure for the development of compounds of the type protriptyline, amitriptyline not only retains the activity but increases it by two fold. It was also our purpose during this work to check whether such similarly prepared arylidene derivatives from the thiazolidinones could be an effective antitubercular compound.

The Schiff bases obtained from the respective amines were reacted in the presence of triethylamine and the respective acid chloride to form the azetidinones. The Schiff

bases were also treated with thioglycollic acid in dry benzene to yield the respective thiazolidinones and these further reacted with benzaldehyde in ethanol in the presence of metallic sodium to form the corresponding aryldenes. The structures of the compounds were characterised using chemical data, elemental analysis, IR, 1HNMR, data wherever necessary.

Antitubercular Screening:

The Compounds were evaluated at 200μg/ml, 100μg/ml, 10μg/ml and 1μg/ml concentrations for their antitubercular activity *in vitro* by using Lowenstein-Jensen (L.J) medium which was inoculated with *M. tuberculosis* $H_{37}Rv$ strain[6]. L.J. medium containing Streptomycin as well as control L.J. medium without any drug was also inoculated with *M. tuberculosis* $H_{37}Rv$ strain and incubated at 37°C for 4 weeks. Readings were taken at the end of 4 weeks.
All the compounds showed activity at 1μg/ml. Thus the presence of the fluro group did not seem to have any role to play in the antitubercular activity.

Experimental

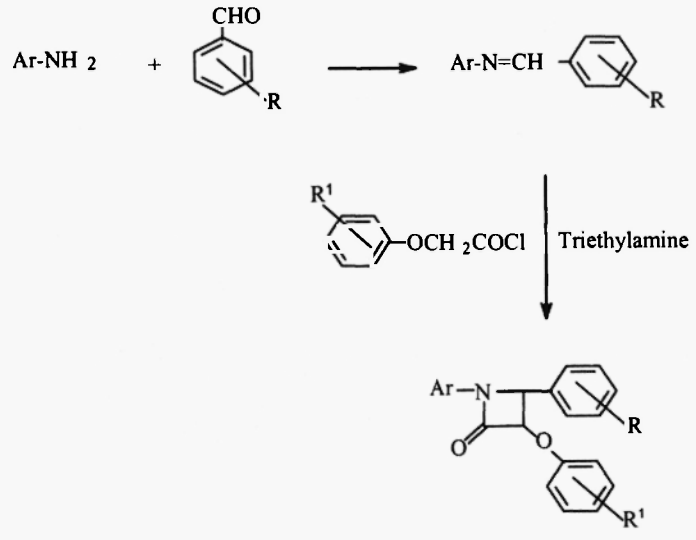
Melting points were determined in open capillaries and are uncorrected. Purity of the compounds was checked by TLC. IR (KBr) spectrum were recorded on Nicolet Magna IR 550 series II spectrophotometers. Combustion analysis reports were within the range of permissible errors.

General method for the Preparation of Schiff bases[7]

Equimolar quantities of corresponding aromatic amine (0.01M) and aromatic aldehyde (0.01M) were dissolved in dry benzene (30ml) in a round botton flask. A pinch of fused zinc chloride was added to hasten the reaction. A Dean-Stark water separator was attached and the reaction mixture was heated till the theoretical amount of water separated out. Excess of benzene was removed under reduced pressure. The solid mass that separated out was filtered and crystallized from aqueous ethanol (80%).

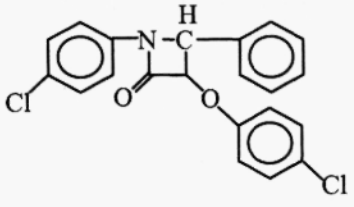
Preparation of Azetidin-2-ones[8]

To a solution of the Schiff base (0.01M) in dry benzene, triethyl amine (0.005M) was added. To this, a solution of aryl acid chloride (0.01M) was added dropwise with stirring. The mixture was then refluxed for a period of three hours. The triethylamine hydrochloride formed was filtered and washed several times with dry benzene. The filtrate and the washings were mixed and concentrated under reduced pressure. The residue obtained was washed with petroleum ether (40-60°C) to remove the unreacted Schiff base and the solid obtained was crystallized from ethanol.
The purity of azetidin-2-ones were established by single spot on the TLC plate. [Benzene: Methanol (95:5)].



Ar = 3-chloro 4-fluoro phenyl
Ar = 2 thiazolyl
Ar = 4-chloro phenyl
Ar = 4-sulphanilamido phenyl

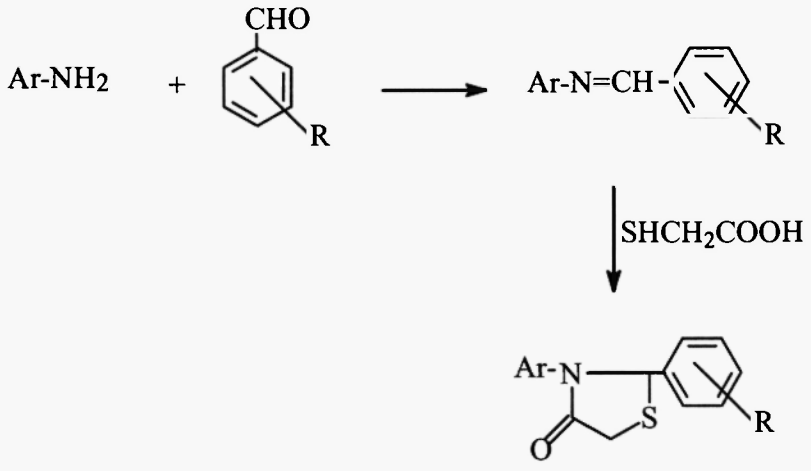
Spectral data: 1-[4-chloro phenyl] 3-phenoxy 4-[4-chloro phenyl] azetidin-2-one.



UV: 276 nm, **IR**: C=O – 1663, C-N – 1404, C-O-C – 1077. **PMR**: Aromatic protons – 6.9 to 8.2 (multiplet), N-CH – 4.5-4.7 (doublet).

General Method of Preparation of Thiazolidine-4-one[8]

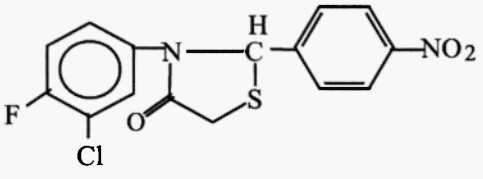
The Schiff base (0.1 mole) and the thioglycollic acid (0.15 mole) were dissolved in dry benzene with vigorous stirring and refluxed for a period of 12 hrs. A pinch of zinc chloride was added at the start of the reaction. Dean stark water separator was attached to remove the water formed during the reaction. Unreacted thioglycollic acid was removed by the addition of saturated sodium bicarbonate solution.



Ar = 3-chloro-4-fluoro phenyl
Ar = 2- thiazolyl
Ar = 4-chloro phenyl
Ar = 4-sulphanilamidophenyl

Spectral Data: Thiazolidin-4-one derived from 3-chloro 4-fluoro aniline

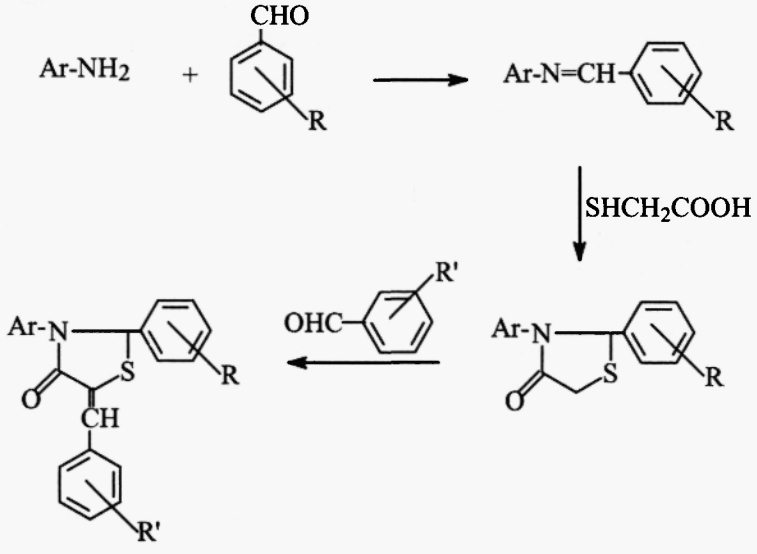
3-[3-chloro, 4-fluoro phenyl] 2-[4-nitrophenyl] thiazolidin-4-one



UV: 275; **IR**: C=O Str – 1692, C-NO_2 – 1600, C-N – 1426, Subst. Aromatic – 811, 838; **PMR**: C-H (methine) – 3.4 (singlet), Aromatic – 6.6 to 8.4 (multiplet), CH_2 – 4 (methine).

General Method of Preparation of Arylidene derivatives[8] of 4-thiazolidinones

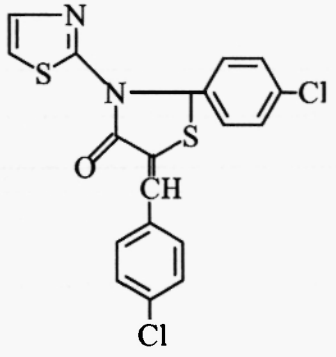
Metallic sodium (0.01M) was added to ethanol (99%, 25ml) with external cooling. After 30 minutes, thiazolidinone (0.01M) was added and the mixture was refluxed for 5 minutes followed by the addition of benzaldehyde (0.01M) in ethanol (99%, 30ml). The contents were then refluxed for 45 min, cooled, poured into ice water and acidified with glacial acetic acid. The solid obtained was filtered (Bhatt J.J. et al.,



1994).

Ar = 3-chloro 4-fluoro phenyl
Ar = 2-thiazolyl
Ar = 4-chloro phenyl

Spectral data: (4-chlorobenzylidine)3-thiazolyl-2-(4-chloro) phenyl - thiazolidinone



UV: 365nm; **IR**: Aromatic C-H – 2957, N-C-O – 1672, Subs. Aromatic – 812, C=N – 1449, C=C – 1586; **PMR**: N-CH – 3.2 to 3.5, Aromatic, C=CH – 5.2.

Results and Discussion:

Antibacterial activity

Azetidinone and thiazolidinones derived from sulphanilamide proved to be totally ineffective. However the arylidene derivative obtained from thiazolidinone (BAr_a1) exhibited antibacterial activity at 1 μg/ml.

The above observation is in coherence to our earlier observation that a compounds having antitubercular activity need not necessarily exhibit any antibacterial activity. We hold the view, that the structure of the bacterial cell wall is being much different from that of the Mycobacteria, the activity can differ.

Antitubercular activity:

All the compounds screened at 200, 100, 10 and 1 μg/ml were active against tubercular bacilli. The structural variation starting from 4-chloro, (3-chloro, 4-fluoro) showed activity both with thiazolidinone and azetidinone moieties respectively. The incorporation of a thiazole moiety was also justified as all the derivatives proved to be effective irrespective of substitutions in the phenyl ring attached to the thiazolidinone or azetidinone moiety. Similarly incorporation of the sulphanamide grouping proved to be equally effective for activity, irrespective of whether the compound contained a thiazolidinone or azetidinone rings and with different substitutions at the phenyl ring attached to these and further a substitution at the fifth position with an arylidine group brings about similar effect.

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