SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF 4-THIAZOLIDINONE AND 2-AZETIDINONE DERIVATIVES

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Synthesis of new 1-(4-substituted phenylimino)-1-(4-hydroxyphenyl)propanes has been done successfully. These Schiff bases were converted to 3-ethyl-3(4-hydroxyphenyl)-2-(4-substituted phenyl)isothiazolidin-4-one and 3-chloro-1-(4-substituted phenyl)-4-ethyl-(4-hydroxyphenyl)azetidin-2-one derivatives with thioglycolic acid and chloroacetyl chloride/Et_3N mixture in 1,4-dioxane, respectively. All the synthesized compounds were screened for biological activities.

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Introduction

Schiff bases are condensation products of primary amines and carbonyl compounds,[1] and they were discovered by the Nobel Prize winner, Hugo Schiff in 1864.[2] Schiff bases (also known as imine or azomethine) are the analogs of the ketones or aldehydes in which the carbonyl group (C=O) has been replaced by azomethine group.[3]

Schiff bases are characterized by the presence of an imine group –N=CH-, in their structure which takes part transamination and racemization reactions in biological system.[1] It exhibits an antibacterial and antifungal effect in their biological properties.[4-5] Metal-imine complexes have been widely investigated due to their antitumor and herbicidal activities. They can work as models for biologically important species.[4]

4-Thiazolidinone and 2-azetidinone derivative constitute an important class of heterocyclic compounds having unique importance due to the broad spectrum of pharmacological activities. They were reported to possess antibacterial and antifungal,[6-8] antitubercular[9] and anti-allergic activity.[10]

4-Thiazolidinones and 2-azetidinones have been synthesized by the condensation of 4,4'-diamino-diphenylsulphone with various aromatic or heterocyclic aldehydes to yield the Schiff's bases,[11] then cyclocondensation of these Schiff's bases with 2-mercaptopropionic acid afforded 4-thiazolidinone derivatives.[12]

In a present study 4-hydroxypropiophenone/3,5-diiodo-4-hydroxypropiophenone treated with primary aromatic amines to form Schiff's bases,[13] then the Schiff's bases on cyclization with thioglycolic acid in 1,4-dioxane gave 4-thiazolidinone derivatives.[14]

Similarly, the reaction of the Schiff bases with chloroacetyl chloride in triethylamine and 1,4 dioxane afforded the corresponding 2-azetidinone derivatives.

All the synthesized compounds were confirmed by IR, ^1H NMR, and mass spectra. The synthesized compounds were screened for antibacterial (*Staphylococcus aureus*, *Escherichia coli*).

Experimental

Melting points were determined in open glass capillaries and were found to be uncorrected. The purity of compounds was checked by TLC. IR spectra were recorded in KBr on a Perkin Elmer spectrometer, 1H NMR spectra were recorded in CD_3OD as solvent and TMS was used as an internal standard. Elemental analysis was carried out on Carlo Erba 1108 analyzer. All reagents were purchased from Aldrich and S.D fine.

Synthesis of Schiff's bases

A mixture of 0.01 mol 4-hydroxypropiophenone and 0.01 mol aromatic amine were dissolved in minimum amount of ethanol and refluxed for 3-4 h. The reaction mixture was cooled and poured onto ice water. The solid was filtered, dried and recrystallized from ethanol.

Synthesis of 4-thiazolidinone derivatives (2a-2f)

Schiff's bases (**1a-1f**) 0.01 mmol and 0.01 mmol thioglycolic acid were dissolved in 15 ml of 1,4-dioxane and refluxed for 9-10 h. The completion of the reaction was checked by TLC. The obtained product was poured onto ice, and the solid was filtered off. The separated solid was washed with sodium bicarbonate solution and dried overnight and weighed.

Synthesis of 2-azitidinone derivatives (3a, 3b)

In a 50 ml beaker were taken 0.1 ml (0.001 mol) chloroacetyl chloride and 15 ml of 1,4-dioxane. In another beaker were taken take 0.3ml (0.003 mol) triethylamine, 15 ml of 1,4-dioxane and 0.01 mol of Schiff's base (**1a** or **1b**). Both the beakers were kept in an ice bath to maintain the temperature about 0 ^{0}C. The chloroacetyl chloride solution was slowly added to the Schiff's base solution with constant stirring between 0 and 5 °C. The reaction mixture was stirred for six hours at room temperature. On completion of reaction (TLC) the excess of dioxane removed by evaporated. The residue was poured onto water. The resulting solid was filtered, washed with water and recrystallized from chloroform.

3-Ethyl-3-(4-hydroxyphenyl)-2-[4-chlorophenyl]iosthiazolidin-4-one (2a)

Light yellow, M.F.$C_{17}H_{16}O_2N_1SCl$, M.W. 333.5, Yield: 62 % , Anal. calcd; C: 61.16, H; 4.79, N; 4.19, S; 9.59, Cl; 10.64. ^{1}H NMR; 7.05(m, CHbenzene), 6.68-6.95 (m, CHbenzene) 4.9-5.0-(s, 1H, aromC-OH), 3.72-(s, 2H, -CH_2), 2.09 (q, 2H, -CH_2), 0.96 (t, 3H,-CH_3), IR KBr cm^{-1} : 1651(C=O), 1605(-CH_2- bend.), 1358(C-N), 993(aromCH=).

3-Ethyl-3-(4-hydroxyphenyl)-2-[pyridine-2yl]-iosthiazolidin-4-one (2b)

White yellow, M.F.$C_{16}H_{16}O_2N_2S$, M.W. 300.0, Yield: 64 %, Anal. calcd; C: 66.89, H; 5.92, N; 4.87, S; 11.14. ^{1}H NMR; 8.07-8.1 (m, CHbenzene), 6.68-6.95 (m, CHbenzene) 4.9-5.0-(s, 1H, aromC-OH), 3.72-(s, 2H,-CH_2), 2.09--(q, 2H, -CH_2), 0.96--(t, 3H,-CH_3), IR KBr cm^{-1}: 1689(C=O), 1605(-CH_2- bend.), 1357 (C-N), 800 (=CHarom).

3-Ethyl-3-(4-hydroxyphenyl)-2-[4-methoxyphenyl]-iosthiazolidin-4-one (2c)

Brown, M.F. $C_{18}H_{19}O_3N_1S$, M.W. 329.0, Yield: 52 % , Anal. calcd; C: 65.65, H; 5.77, N; 4.25, S; 9.72. ^{1}H NMR; 7.12(m, CHbenzene), 6.49-6.77(m, CH benzene), 4.9-5.0(s, 1H, aromC-OH), 3.71(s, 2H,-CH_2), 3.83(s, 3H-CH_3), 2.09(q,2H, -CH_2), 0.96(t, 3H, -CH_3), IR KBr, cm^{-1} : 1648(C=O), 1605(-CH_2- bend.), 1354(C-N), 990(=CHarom).

3-Ethyl-3-(4-hydroxyphenyl)-2-[4-methylphenyl]isothiazo1idin-4-one (2d)

White yellow, M.F.$C_{18}H_{19}O_2N_1S$, M.W. 329.0, Yield: 52 % , Anal. calcd; C: 69.009, H; 6.0702, N; 4.4728, S; 10.2236. ^{1}H NMR; 7.01(m, CHbenzene), 6.49-7.12 (m, CHbenzene) 4.9-5.0(s, 1H, aromC-OH), 3.77(s, 2H, -CH_2), 2.34 (s,3H-CH_3), 2.09(q, 2H, -CH_2), 0.96(t, 3H, -CH_3), IR KBr, cm^{-1}: 1648(C=O), 1605(-CH_2- bend.), 1354-(C-N), 990-(aromCH=).

3-Ethyl-3-(4-hydroxyphenyl)-2-[4-nitrophenyl]isothiazolidin-4-one (2e)

Yellow, M.F.$C_{17}H_{16}O_4N_2S$, M.W. 344.0, Yield: 62.34 %, Anal. calcd; C: 59.30, H; 4.65, N; 8.14, S; 9.30 ^{1}H NMR; 8.04(m, CHbenzene), 6.70-7.12(m, CHbenzene) 4.9-5.0(s, 1H, aromC-OH), 3.77(s, 2H,-CH_2), 2.34 (q, 2H, -CH_2), 0.96 (t, 3H,-CH_3), IR KBr cm^{-1}: 1689(C=O), 1605(-CH_2-, bend.), 1358-(C-N), 993-(=CHarom).

3-Ethyl-3-(3,5-diiodo-4-hydroxyphenyl)-2-[4-methoxyphenyl]-iosthiazolidin-4-one (2f)

Brown, M.F. $C_{17}H_{14}O_2N_1SI_2Cl$, M.W. 543.50, Yield: 49 % , Anal. calcd; C: 65.65, H; 5.77, N; 4.25, S; 9.72. ^{1}H NMR; 7.52(m, CHbenzene), 6.27-6.70(m, CHbenzene) 4.9-5.0(s, 1H, aromC-OH), 3.71(s, 2H, -CH_2), 2.09(q, 2H, CH_2), 0.96(t, 3H, -CH_3), IR KBr cm^{-1}: 1648(C=O), 1605(-CH_2-bend.), 1354-(C-N), 990-(aromCH=).

3-Chloro-1-(4-chlorophenyl)-4-ethyl-(4-hydroxyphenyl)azetidin-2-one (3a)

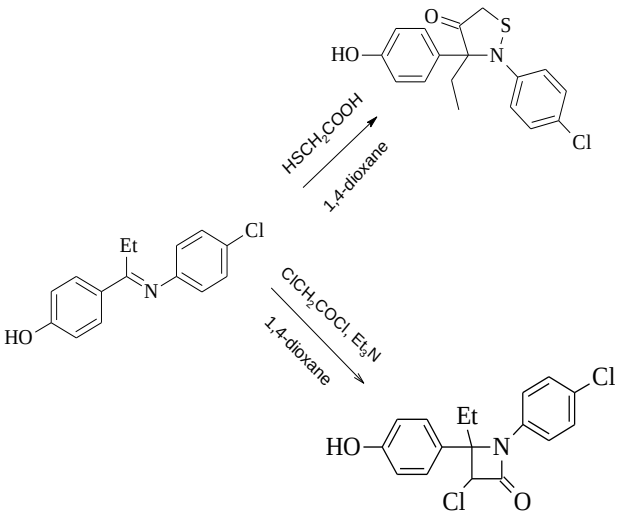
Brown yellow, M.F.$C_{17}H_{15}O_2NCl_2$, M.W. 336.00, Yield: 51.76 % , Anal. calcd; C: 60.7145, H; 4.642, N; 4.1666, Cl; 21.1309. ^{1}H NMR; 7.04-7.32(m, CHbenzene), 6.65-6.96- (m, CHbenzene), 4.9-5.0(s, 1H, aromC-OH), 5.43(s, 1H, -CH), 1.73(q, 2H, -CH_2), 0.96(t, 3H, -CH_3), IR KBr, cm^{-1}: 1649(C=O), 1605(-CH_2- bend.), 1357-(C-N), 993-(aromCH=).

3-Chloro-4-ethyl-(4-hydroxyphenyl)-1-(pyridine-2-yl)azetidin-2-one (3b)

White yellow, M.F. $C_{17}H_{15}O_2N_2Cl$, M.W. 314.5, Yield: 60.00 %, Anal. calcd; C: 4.86, H; 4.77, N; 8.90, Cl; 11.29. ^{1}H NMR; 8.05-8.1(m, CHbenzene), 6.65-6.96(m, CHbenzene) 4.9-5.0(s, 1H, arom.C-OH), 5.43(s, 1H, -CH), 1.73(q, 2H, -CH_2), 0.96(t, 3H, -CH_3), IR KBr, cm^{-1}: 1689(C=O), 1605(-CH_2- bend.), 1351-(C-N), 800-(aromCH=).

Result and discussion

The Schiff base precursors (**1a-1f**) were prepared in the reaction of 4-hydroxypropiophenone and amine compounds in ethanol under 3-4 h reflux according to the ususal procedure. These Schiff's bases on cyclocondensation reaction in 1,4-dioxane with thioglycolic acid and 1-chloroacetyl chloride afforded 4-thiazolidinone (**2a-2f**) and 2-azitidinone (**3a, 3b**) derivatives, respectively. For example, the compound **1** could be transformed into **2a** and **3a** with thioglycolic acid and chlorocetyl chloride/Et_3N in 1,4-dioxane with 62 and 51 % yield, respectively.



Scheme 1. Synthesis of the isothiazolidinone (**2a-2f**) and azetidinone (**3a** and **3b**) compounds

The structure of the formed compounds (**2a-f** and **3a,3b**) were confirmed by elemental analysis, IR and NMR spectral studies. All of these compound show the band at 1690 cm^{-1} belong to the the cyclic C=O group.

Antibacterial activity of compounds

The synthesized compounds were subjected to antibacterial studies using Staphylococcus aureus and E. Coli bacteria and the results were expressed regarding zones of inhibition.

The antibacterial activity of the series has been carried out against some strain of bacteria. The result shows that the prepared compounds are toxic to bacteria and found to be more active against the above microbes. The comparison of the antibacterial activity of these compounds with penicillin and sulphanylamide shows that these compounds have almost similar activity.

Table 1. Antimicrobial effect of the synthesized compounds (**2a-f** and **3a**, **3b**)

	Zone of inhibition in mm	
Compound	**Staphylococcus aureus**	**E. Coli**
2a	18	16
2b	12	14
2c	18	21
2d	22	24
2e	16	14
2f	17	19
3a	21	18
3b	16	26

Conclusion

The present work describes the synthesis of Schiff's bases, 4-thiazolidinone, and 2-azetidinone derivatives were prepared and reaction completion was confirmed by TLC and synthesized compounds purified by recrystallization. The structure of synthesized compounds assigned by on the basis of the spectral data elemental analysis, IR spectral studies and NMR spectral studies and these compound shows the band at 1690cm^{-1} for the cyclic C=O group. All these compounds show the NMR signal for different kinds of positions at the respective position.

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