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Synthesis of Some New 2-Methyl -1,4-benzothiazine-3(1*H*)-one Derivatives as Potential Vasodilators

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Abstract The increase in the internal diameter of a blood vessel that results from relaxation of smooth muscle within the wall of the vessel is vasodilation. This causes an increase in blood flow and a decrease in systemic vascular resistance. Some substances produced by tissue deprived of fresh blood seem to be responsible for the dilation. Many products of metabolism bring about the action, CO₂ and acids are among them. Dilation of vessels is necessary to restore local environment of tissues and normal metabolism. It may prove to be potential in the treatment of different cardiac disorders like atherosclerosis, where, the blood vessels are narrowed due to deposition of plaque of substances like cholesterol etc. 1,4-benzothiazines have been reported to possess wide range of pharmacological and biological activities. Here, we report the synthesis and biological activity of some new arylidenehydrazino-(1*H*)-1,4-benzothiazines. The synthesized compounds were subjected to a prediction of biological activities. A software application (PASS) was used for this purpose. The relationship between structure and different biological activities was studied and it was found that the arylidenehydrazino-(1*H*)-1,4-benzothiazines are expected to be potential vasodilators.

Key words :Potential Vasodilator

Introduction

2-Methyl-1,4-benzothiazine-3(1*H*)-one (1) was obtained by refluxing 2-aminothiophenol and methyl 2-chloropropionate in 33% NaOH. The compound 1 was reacted with hydrazine hydrate in methanol to get 3-hydrazino-2-methyl-(1*H*)-1,4-benzothiazine (2), which when reacted with various substituted aldehydes furnished arylidenehydrazino-(1*H*)-1,4-benzothiazine (3). [Scheme]

SCHEME

Experimental

Melting points were taken in an open capillary tube and are uncorrected. IR spectra (KBr/Nujol) were recorded on a Perkin-Elmer 783 spectrophotometer and PMR spectra ($DMSO-d_6/CDCl_3$) on a Bruker Ac 300F spectrometer (300MHz) using TMS as an internal standard. The mass spectra were recorded by EIMS technique on an Autospec mass spectrometer. The progress¹⁻⁵ of reaction and purity of samples were checked by TLC using silica gel G.

Synthesis of 2-methyl-1,4-benzothiazine-3(1H)-one (1):

A mixture of 2-aminothiophenol (2g, 0.016 mol) and methyl 2-chloropropionate (1.96g, 0.016 mol) containing 33% NaOH (17.5 ml) was refluxed on a steam bath for 5hrs. The reaction mixture was then cooled, neutralized with dilute HCl and the precipitated solid was filtered, washed with water and recrystallized from 80% ethanol. Yield: 2g, (69%). M.P. 125°C. Elemental analysis: Found: C, 61.25; H, 4.84; N, 6.93%. for C_9H_9ONS Required C, 60.34; H, 5.03; N, 7.82%. IR(KBr): ν_{max} 3220(NH), 1700-1650 cm^{-1} (cyclic $>C=O$). PMR($CDCl_3$): δ 1.5(3H, d, $CHCH_3$), 3.5-3.6(1H, q, $CHCH_3$), 6.9-7.35(4H, m, Ar-H), 9.2-9.3 ppm (1H, s, exchangeable with D_2O , NH).

Synthesis of 3-hydrazino-2-methyl-1,4-benzothiazine (2):

A mixture of 1 (1.44g, 0.008 mol) and hydrazine hydrate (0.4g, 0.008 mol) in methanol (10 ml) was heated on a steam bath at 70-80°C for 2hrs. The reaction mixture was concentrated and cooled to get a white crystalline product. Yield: 0.83g, (83%); M.P. 110°C. Elemental Analysis: Found: C, 56.46; H, 4.87; N, 22.57%. for $C_9H_{11}N_3S$, Required C, 55.95; H, 5.77; N, 21.76%. IR(KBr): ν_{max} 3312-3100 (NHNH₂), 1665 cm^{-1} ($>C=N$).

Synthesis of 3-[arylidinehydrazino]-1H-1,4-benzothiazine (3a-h):

A mixture of 2 (0.12g, 0.006 mol) and substituted aldehyde or ketone (0.006 mol) in methanol (10 ml) was refluxed in presence of acetic acid (2-3 drops) on a steam bath for 3hrs. The reaction mixture was cooled and concentrated to get a white crystalline product. Yield: varied from (26-95%). Additional analytical data is given in TABLE 1. 3a: IR (KBr): ν_{max} 3200-3100 (NH), 1620 ($>C=N$), 1600 cm^{-1} (C=C). PMR ($CDCl_3$): δ 1.4-1.5 (3H, d, $CHCH_3$), 3.53-3.6 (1H, q, $CHCH_3$), 3.94 (3H, s, OCH_3), 6.63 (1H, br. s, OH exchangeable with D_2O), 6.93-7.43(7H, m, Ar-H), 9.51(1H, s, NH exchangeable with D_2O), 9.82(1H, s, N=CH). 3b: IR (KBr): ν_{max} 3100-3200 (NH), 1620 cm^{-1} ($>C=N$). 3c: IR (KBr): ν_{max} 3100-3300 (NH), 1615 cm^{-1} ($>C=N$). 3d: IR (KBr): ν_{max} 3050-3250 (NH), 1615 ($>C=N$), 1050 cm^{-1} (C-O-C). 3e: IR (KBr): ν_{max} 3200 (NH), 1690-1590 ($>C=N$), 1600 cm^{-1} (C=C). 3f: IR (KBr): ν_{max} 3500-3250 (OH or NH), 1625 ($>C=N$), 1600 cm^{-1} (C=C). 3g: IR (KBr): ν_{max} 3550-3250 (NH), 1620 ($>C=N$), 1600 cm^{-1} ($>C=C$). 3h: IR (KBr): ν_{max} 3540 (NH), 1620 ($>C=N$), 1600 cm^{-1} (C=C).

Prediction of biological activities

The compounds 3a-3h were studied for the predictions of their probabilities of being active [Pa] and inactive [Pi] for the selected activities such that the $Pa > 70\%$. A software application (PASS) was used for this purpose. The relationship between structure and different biological activities was studied. It was found that 3-[arylidinehydrazino]-1H-1,4-benzothiazine (3a-h) are expected to exhibit spectacular vasodilator activity.

Conclusion

The comparison between their probabilities of being active as a potential vasodilator revealed that the compound 3-[3,4,5-trimethoxy phenylidenehydrazino]-1H-1,4-benzothiazine (3d) shows spectacular vasodilator activity. Hence this compound has been recommended for the screening of the vasodilator activity.

TABLE 1. Physical data for compound [3a-h]

<i>Comp.</i>	R	Mol formula	Mp.^oC	Elemental Analysis (%)	
				Found	Required
3a	3-OH, 2-OCH₃	C₁₇H₁₇O₂N₃S	100	C, 63.07; H, 4.78; N, 13.15	C, 62.38; H, 5.19; N, 12.84
b	2-NO₂	C₁₆H₁₄O₂N₄S	90	C, 59.28; H, 4.78; N, 16.88	C, 58.89; H, 4.29; N, 17.17
c	4-OH	C₁₆H₁₃ON₃S	122	C, 65.35; H, 4.86; N, 13.10	C, 64.64; H, 5.05; N, 14.14
d	3,4,5(OCH₃)₃	C₁₉H₂₁O₃N₃S	104	C, 62.14; H, 5.17; N, 12.21	C, 61.45; H, 5.66; N, 11.32
e	4-Cl	C₁₆H₁₄N₃SCl	138	C, 61.76; H, 4.12; N, 12.62	C, 60.85; H, 4.43; N, 13.31
f	3-OH,C₆H₄	C₁₆H₁₃ON₃S	70	C, 63.83; H, 4.94; N, 13.75	C, 64.64; H, 5.05; N, 14.14
g	2-OH,C₆H₄	C₁₆H₁₃ON₃S	134	C, 63.82; H, 4.86; N, 15.06	C, 64.64; H, 5.05; N, 14.14
h	4-CH₃,C₆H₄	C₁₇H₁₇ON₃S	113	C, 64.78; H, 6.15; N, 12.82	C, 65.59; H, 5.46; N, 13.50

comp	Pa	Pi
3a	0.77	0.01
3b	0.833	0.007
3c	0.797	0.008
3d	0.838	0.007
3e	0.802	0.008
3f	0.796	0.008
3g	0.77	0.009
3h	0.833	0.007

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