Research Paper

Synthesis and Characterization of Benzothiazine Analogues

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ABSTRACT:

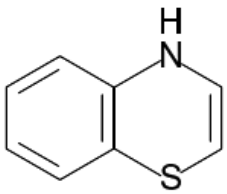
Benzene joins a 1,4-thiazine ring to form benzothiazines, an important group of heterocycles. As part of our ongoing research into new ways to make molecules that have biological effects, we were interested in making different heterocyclic structures with thiazine rings. This is due to the fact that heterocyclic structures are a necessary component of many physiologically active, naturally occurring compounds. We have created a quick, solvent-free synthesis technique for the oxidative cyclo condensation of 2-amino benzenethiol and 1, 3-dicarbonyl using a catalytic quantity of hydrazine hydrate. In order to generate a high yield of 2,3-disubstituted-1,4-benzothiazines, this technique was developed.

Keywords: Synthesis, Benzothiazine, 2-aminobenzenethiol, 4H-1, 4-Benzothiazines.

INTRODUCTION:

Medicinal chemistry is very interested in benzothiazine analogues because they have many biological effects, such as antibacterial, anti-inflammatory, anticancer, and antioxidant effects (1). There is only one benzothiazine ring system in the world. It is made up of a benzene ring fused with a thiazine ring. This gives it special chemical and biological properties.

Throughout the years, alterations to this fundamental structure have resulted in the creation of several derivatives with improved pharmacological properties (2). We must purposefully alter the core structure to create benzothiazine analogues. These changes can be made through nucleophilic substitution, cyclization, or oxidation. We plan how to make these compounds so that they have the highest yield and selectivity, and we add functional groups that make them more bioactive (3). When people make new benzothiazine derivatives, they often want to improve their solubility, stability, and target specificity, all of which are important for making medicines that work well (4). Characterizing benzothiazine analogues is an important part of the development process because it gives information about the molecules' structure, purity, and physical properties. An NMR spectrometer, an MS spectrometer, an IR spectrometer, and an X-ray crystallography are some of the tools that are used to look at the molecular structure and chemical integrity of substances (5). High-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC) are also often used to check for purity and find byproducts made during synthesis. We must make benzothiazine-derived compounds efficiently and thoroughly characterize them for medical use (6). This project investigated how to make new benzothiazine analogues and characterized them by checking their chemical and structural properties and considering their medical uses (7).



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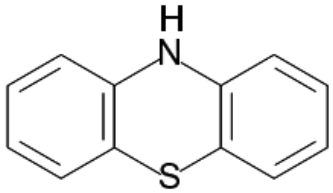

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1,4-Benzothiazine derivatives have many medical and biological effects, such as killing fungi, boosting the immune system, treating rheumatism and other rheumatic conditions, relaxing blood vessels, blocking aldose reductase, stopping irregular heartbeats, protecting neurons, killing parasites and bacteria, fighting viruses and bacteria, lowering blood pressure, reducing inflammation, fighting depression, fighting tumors, lowering fever, increasing urine production, and fighting tuberculosis— all of these and more (8, 9). The properties imply that 1,4-benzothiazine is a viable template for therapeutic applications and medicinal chemistry. Dyes and photography use 1,4-derivatives of benzothiazine. Their typical preparation process involves the use of either expensive and dangerous solvents or lachrymatory halo organic substrates (10). Our main goal is to come up with a safe and long-lasting way to make 4H-1,4-benzothiazine derivatives, keeping in mind the different ways that these bioactive thiazine derivatives can be used. Many researchers have reported the synthesis of 4H-1,4-

benzothiazine with the aid of microwaves (11). It is possible to make 1,4-benzothiazines by mixing 2-aminobenzene thiol with ethyl 2-chloroacetoacetate in ethanol (12).

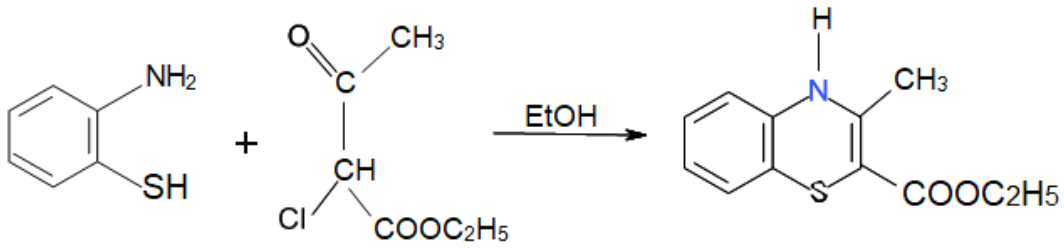


Figure 1: Synthesis of 4H-1,4-Benzothiazines

A rapid, solvent-free synthesis technique for the oxidative cyclo-condensation of 2-amino benzenethiol and 1,3-dicarbonyl using a catalytic quantity of hydrazine hydrate has been developed in order to create 2,3-disubstituted-1,4-benzothiazines in high yield (figure 2) (13, 14)

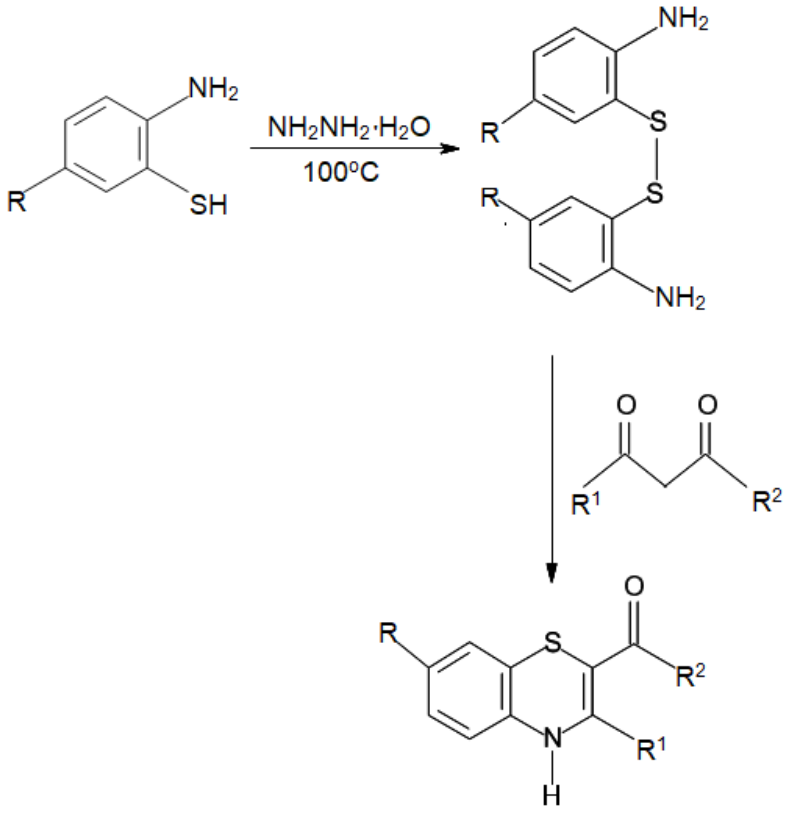


Figure 2: 2, 3-disubstituted-1,4-benzothiazines

Typically, 2-aminobenzene thiol reacted with α-haloketones or α-haloesters to create 1,4-benzothiazines; however, the primary disadvantage of this process was the lachrymatory nature of the latter (15). The process for producing 1, 4-benzo-thiazines has been marginally enhanced in recent years. In the presence of DMSO, substituted 2-amino benzene thiol

undergoes oxidative condensation with β-diketones and β-ketoesters (16, 17). The latter has both solvent and oxidant qualities and is a dipolar aprotic solvent. It contains several negative features, and it is difficult to separate the product from it. Therefore, this strategy needs to be improved (18). The mechanism of the reaction between β-diketones/β-ketoesters and substituted 2-aminobenzenethiols involves two stages (19). First, 2-aminobenzenethiols are oxidized by DMSO to their corresponding disulfide derivatives, which then condense with β-diketones and β-keto esters to produce 4H-1, 4-benzothiazines in the second phase. According to the literature review, 2-aminobenzenethiols are readily oxidized by hydrogen peroxide, sodium perborate, thallium acetate, DMSO-iodine, a combination of NO_2 and NO_3, and even ambient oxygen when left in the presence of a little quantity of base (20-28).

MATERIAL AND METHODS:

The reactions were conducted in a household microwave oven. All the analytical and physical data for the synthesized substances align well with their literature values (29).

Synthesis of substituted 4H-1, 4-benzothiazines

DMF (5 mmol), catalytic hydrazine hydrate (1 mmol), and substituted 2-amino benzenethiol (10 mmol) were mixed together and put through microwaves for 30 seconds. After adding 10 mmol of β-diketone to the reaction mixture, it is microwaved again and again for three minutes, with breaks of thirty seconds (30-38). After monitoring the reaction's conclusion with TLC, we cooled the reaction mixture and placed it on crushed ice. After filtering and washing with 50% ethanol, the isolated material crystallized from the ethanol (Figure 3) (39, 52).

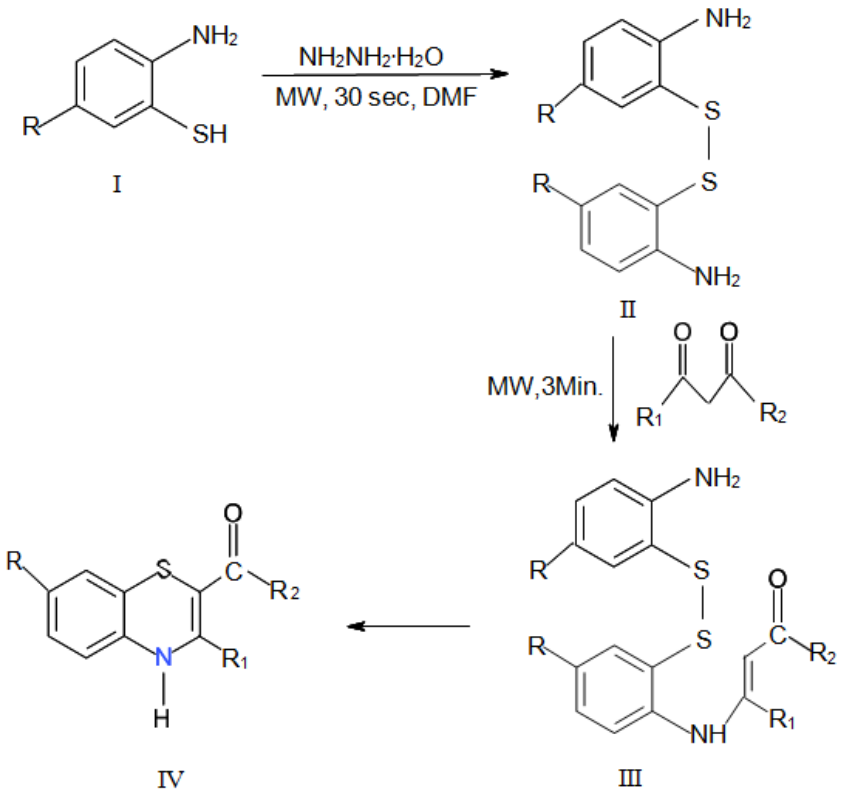
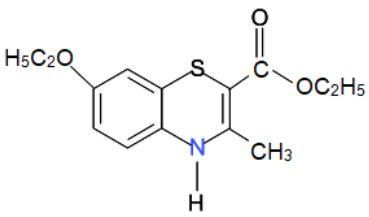
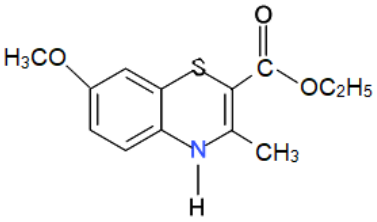


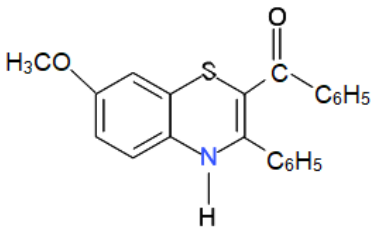
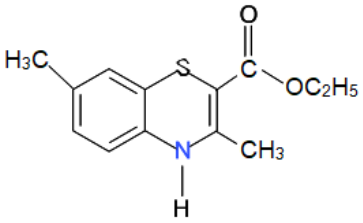
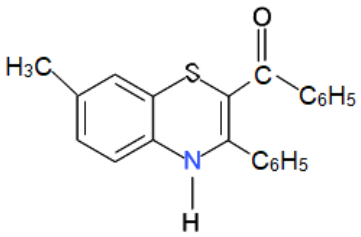
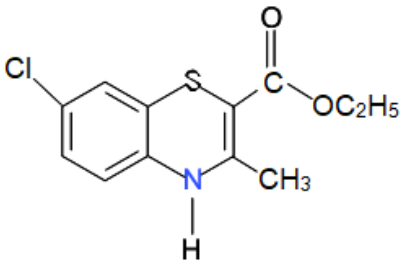
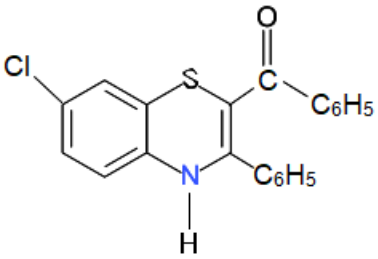
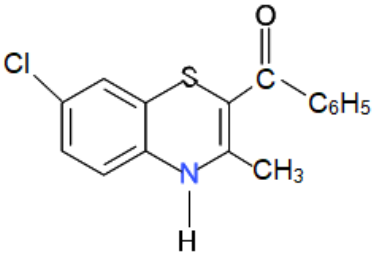
Figure 3: Synthetic scheme of 1, 4-benzothiazines analogues

RESULT AND DISCUSSION:

In present investigation following 1, 4-benzothiazines analogues have been synthesized:

Table 1: Physical data of the synthesized benzothiazines derivatives

Sr. No	Name	Structure	MP	Mol Formula	Yield
1	7-Ethoxy-2-ethoxycarbonyl-3-methyl-4H-1,4-benzothiazine		103^{0}C	$C_{14}H_{17}O_3NS$	70%
2	2-Ethoxycarbonyl-7-methoxy-3-methyl-4H-1,4-benzothiazine		119^{0}C	$C_{13}H_{15}O_3NS$	65%

3	2-Benzoyl-7-methoxy-3-phenyl-4H-1,4-benzothiazine		172^{0}C	$C_{22}H_{17}O_2NS$	82%
4	2-Ethoxycarbonyl-3,7-dimethyl-4H-1,4-benzothiazine		178^{0}C	$C_{13}H_{15}O_2NS$	75%
5	2-Benzoyl-7-methyl-3-phenyl-4H-1,4-benzothiazine		194^{0}C	$C_{22}H_{17}ONS$	80%
6	7-Chloro-2-ethoxycarbonyl-3-methyl-4H-1,4-benzothiazine		181^{0}C	$C_{12}H_{12}O_2NSCl$	75%
7	2-Benzoyl-7-chloro-3-phenyl-4H-1,4-benzothiazine		87^{0}C	$C_{21}H_{14}ONSCl$	85%
8	2-Benzoyl-7-chloro-3-methyl-4H-1,4-benzothiazine		245^{0}C	$C_{16}H_{12}ONSCl$	85%

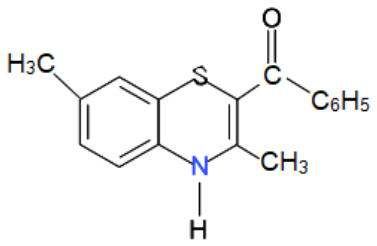
9	2-Benzoyl-3,7-dimethyl-4H-1,4-benzothiazine		207^{0}C	$C_{17}H_{15}ONS$	90%

Table 2: Analytical data of the synthesized benzothiazines derivatives

Mol No	IR	NMR	Mass
1	IR (KBr, ν_{max}, cm^{-1}): 3410(N-H), 1685 (>C=O), 1460, 1350(C-CH_3), 1230, 1035(C-O-C), 855, 835 (adj.2H in ring), 3000 (C-Haliph.)	^{1}HNMR ($CDCl_3$) δ: 6.85-6.3 (3H, m, Ar.), 4.10(2H, q, CH_2 a tC-2), 1.20(3H, t, CH_3 at C-2), 2.2 (3H, s, CH_3 at C-3), 3.95(2H, q, CH_2 at C-7), 1.40 (3H, t, CH_3 at C-7), 8.75 (1H, s, N-H)	MS (m/z): 279 (M^+), 278 (M^+-H), 251(M^+-C_2H_4), 250 (M^+-C_2H_5), 233 (M^+-C_2H_5OH), 234 (M^+-OC_2H_5), 222 (M^+-COC_2H_5), 205 (M^+-C_2H_5OH, CO). Anal. Calculated (%) for $C_{14}H_{17}O_3NS$: C, 60.21; H, 6.09; N, 5.01.Found (%): C, 60.11; H, 6.08; N, 5.02.
2	IR (KBr, ν_{max}, cm^{-1}):3340(N-H), 1685(>C=O), 1465, 1340(C-CH_3), 1245, 1035(C-O-C), 850, 820 (adj.2Hin ring)	^{1}HNMR ($CDCl_3$) δ: 6.8-6.4 (3H, m, Ar.), 3.95(2H, q, CH_2 at C-2), 2.25 (3H, s, CH_3 at C-3), 1.25(3H, t, CH_3 at C-2), 4.4(3H, s,O-CH_3), 8.8(1H,s,N-H)	MS (m/z): 265(M^+), 264(M^+-H), 235(M^+-CH_2O), 206(M^+-CH_2O, C_2H_5), 178 (M^+-CH_2O, COC_2H_5), 250(M^+-CH_3), 222(M^+-CH_3, CO), 193(M^+-CH_3, CO, C_2H_5), 165(M^+-CH_3, CO, COC_2H_5). Anal. Calculated (%) for: $C_{13}H_{15}O_3NS$: C, 58.86; H, 5.66; N, 5.28. Found (%): C, 58.84; H, 5.67; N, 5.30.
3	IR (KBr, ν_{max}, cm^{-1}): 3400(N-H), 1665 (>C=O), 1230, 1050(C-O-C), 855, 820 (adj.2H in ring), 2920(C-	^{1}HNMR ($CDCl_3$) δ: 7.8-6.95 (13H, m, Ar.), 4.5 (3H, s, OCH_3), 8.7 (1H, s, N-H)	MS (m/z): 359(M^+), 358(M^+-H), 254(M^+-COC_6H_5), 282(M^+-C_6H_5), 329(M^+-CH_2O), 344 (M^+-CH_3), 316 (M^+-CH_3, CO), 252(M^+-CH_2O, C_6H_5), 224 (M^+-CH_2O, COC_6H_5). Anal.

	H,aliph.)		Calculated (%) for $C_{22}H_{17}O_2NS$: C, 70.19; H, 4.73; N, 3.90. Found (%): C, 70.20; H, 4.69; N, 3.88.
4	IR (KBr, ν_{max}, cm^{-1}): 3460 (N-H), 1680 (>C=O), 1465, 1345 (C-CH_3), 1230, 1035 (C-O-C), 855, 825 (adj. 2H in ring), 2980 (C-H aliph.)	^{1}HNMR ($CDCl_3$) δ: 6.7-6.4 (3H, m, Ar.), 4.15 (2H, q, CH_2 at C-2), 2.25 (3H, s, CH_3 at C-3), 1.95 (3H, s, CH_3 at C-7), 1.25 (3H, t, CH_3 at C-2), 8.8 (1H, s, N-H)	MS (m/z): 249(M^+), 248(M^+-H), 220 (M^+-C_2H_5), 204(M^+-OC_2H_5), 192(M^+-COC_2H_5), 221 (M^+-C_2H_4), 203(M^+-C_2H_5OH), 175(M^+-C_2H_5OH, CO). Anal. Calculated (%) for $C_{13}H_{15}O_2NS$: C, 62.65; H, 6.02; N, 5.62. Found (%): C, 62.63; H, 6.63; N, 5.60
5	IR (KBr, ν_{max}, cm^{-1}): 3345 (N-H), 1695 (>C=O), 1470, 1330 (C-CH_3), 865, 820 (adj. 2H in ring), 3055 (C-H, Ar)	^{1}HNMR ($CDCl_3$) δ:7.3-7.0 (13H, m, Ar.), 2.35 (3H, s, CH_3 at C-7), 8.8 (1H, s, NH)	MS (m/z): 343 (M^+), 342 (M^+-H), 238 (M^+-COC_6H_5), 266 (M^+-C_6H_5), 161(M^+-COC_6H_5, C_6H_5). Anal. Calculated (%) for $C_{22}H_{17}ONS$: C, 73.46; H, 4.95; N, 4.08. Found (%): C, 73.75; H, 4.90; N, 4.06
6	IR (KBr, ν_{max}, cm^{-1}): 3380 (N-H), 1690 (>C=O), 1465, 1360 (C-CH_3), 735 (C-Cl), 1240, 1040 (C-O-C), 860,825 (adj. 2H in ring), 2985 (C-H aliph.)	^{1}HNMR ($CDCl_3$) δ: 6.85-6.4 (3H, m, Ar.), 4.05 (2H, q, CH_2 at C-2), 2.25 (3H, s, CH_3 at C-3), 1.25 (3H, t, CH_3 at C-2), 8.7 (1H, s, N-H)	MS (m/z): 269 (M^+), 268 (M^+-H), 241 (M^+-C_2H_4), 224 (M^+-C_2H_4, OH) or (M^+-OC_2H_5), 196 (M^+-$COOC_2H_5$), 240 (M^+-C_2H_5), 223 (M^+-C_2H_5OH), 212(M^+-C_2H_5, CO). Anal. Calculated (%) for $C_{12}H_{12}O_2NSCl$: C, 53.43; H, 4.45; N, 5.19. Found (%): C, 53.39; H, 4.42; N, 5.20
7	IR (KBr, ν_{max}, cm^{-1}):	^{1}HNMR ($CDCl_3$) δ:	MS (m/z): 363 (M^+), 362 (M^+-

	3360 (N-H), 1690 (>C=O), 740 (C-Cl), 850, 820 (adj.2H in ring), 3060 (C-H, Ar)	7.5-6.85 (13H, m, Ar), 8.6 (H, s, N-H)	H), 258 (M^+-COC_6H_5), 286 (M^+-C_6H_5), 77 (M^+-C_6H_5), 181 (M^+- COC_6H_5, C_6H_5), 146 (M^+-COC_6H_5, C_6H_5, Cl) Anal. Calculated (%) for $C_{21}H_{14}ONSCl$: C, 69.32; H, 3.85; N, 3.85. Found (%): C, 69.30; H, 3.90; N, 3.90
8	IR (KBr, ν_{max}, cm^{-1}): 3365 (N-H), 1675 (>C=O), 1460, 1340 (C-CH_3), 725 (C-Cl), 850, 830 (adj. 2H in ring), 3020 (C-H, Ar)	^{1}HNMR ($CDCl_3$) δ: 7.6-7.0 (8H, m, Ar.), 2.25 (3H, s, CH_3 at C-3), 8.7 (1H, s, NH)	MS (m/z): 301 (M^+), 300 (M^+-H), 196 (M^+-COC_6H_5), 224(M^+-C_6H_5), 161 (M^+-COC_6H_5, Cl). Anal. Calculated (%) for: $C_{16}H_{12}ONSCl$: C, 59.70; H, 4.97; N, 4.64.Found (%): C, 59.68; H, 4.89; N, 4.60
9	IR (KBr ν_{max}, cm^{-1}): 3380 (N-H), 1680 (>C=O), 1460, 1340 (C-CH_3), 860, 825 (adj. 2H in ring), 2930 (C-H, aliph.), 3030 (C-H, Ar.)	^{1}HNMR ($CDCl_3$) δ: 7.4-6.6 (8H, m, Ar.), 2.15 (3H, s, CH_3 at C-3), 1.95 (3H, s, CH_3 at C-7), 8.8 (1H, s, NH)	MS (m/z): 281 (M^+), 280 (M^+-H), 204 (M^+-C_6H_5), 176 (M^+-COC_6H_5), 131 (M^+-COC_6H_5, HCS), 144 (M^+-COC_6H_5, S). Anal. Calculated (%) for $C_{17}H_{15}ONS$: C, 72.59; H, 5.33; N, 4.98. Found (%): C, 72.60; H, 5.35; N, 4.95.

Spectral analysis

The IR spectra of the different synthesized 1,4-benzothiazines were all different. The C=O stretching absorption peak was found between 1695 and 1665 cm^{-3}, and the N-H stretching absorption peak was between 3410 and 3340 cm^{-3}. Bending vibrations of C-CH cause the weak absorption bands in the 1470–1330 cm range. Between 1240 and 1225 cm^{-3} and 1030 to 1040 cm^{-3} are the bands that show up in compounds 1, 2, 4, and 6. Asymmetric and symmetric C-O-C vibrations, respectively, cause these bands. A band in the range of 725-740 cm^{-1} is attributed to C-Cl stretching vibrations in compounds 6, 7, and 8. The NMR spectra of

all the compounds show a single broad peak for the N-H proton between 8.70 and 8.80. Protons in the aromatic ring trigger multiplets in the 6.4–7.6 area. Methoxy derivatives have a singlet peak at around 4.4δ because of the $OOCH_3$ group. The multiplicity and anticipated region also show peaks for the C_2H_5 and CH_3 groups. The mass spectra of all 1,4-benzothiazines with a benzoyl group had a peak at m/z = M+-105 (with high intensity) and 105 ($C_6C_6H_9CO^+$ base peak) because the benzoyl group was gone. Peaks were found at m/z = M+M+-C_2H_4M+M+-C_2H_5M+M+-COC_2H_5 and M+M+-OC_2H_5 or the 2-ethoxycarbonyl derivatives.

CONCLUSION:

A 1,4-thiazine ring fused to benzene characterizes benzothiazines, a heterocycle class. We were interested in synthesizing heterocyclic thiazine rings as part of an effort to discover novel synthetic methods for physiologically active compounds. This is because heterocyclic structures are essential to many physiologically active natural substances. We made a quick and easy oxidative cyclo condensation method for 2-amino benzenethiol and 1, 3-dicarbonyl with hydrazine hydrate as a catalyst. We devised this method to produce 2, 3-disubstituted-1,4-benzothiazines in high yield. Different synthesized 4H-1, 4-benzothiazines had different infrared spectra. The C=O and N-H stretching absorption peaks were observed between 1695 and 1665 cm^{-3} and 3410 and 3340 cm^{-3}, respectively. The weak absorption bands in the 1470-1330 cm^{-3} range result from C-CH_3 bending vibrations. Compounds 1, 2, 4, and 6 exhibit bands in the 1240–1225 cm and 1030–1040 cm ranges. These are caused by asymmetric and symmetric C–O–C vibrations. A band at 725-740 cm^{-1} is attributed to C-Cl stretching vibrations in compounds 6, 7, and 8. The NMR spectra of all compounds exhibit a large singlet peak for the N-H proton, around 8.70–88.80. Rotons in the aromatic ring create 6.4–7.6 multiplets. Methoxy derivatives have a singlet peak at 4.4δ due to the $OOCH_3$ group. Both C_2H_5 and CH_3 groups have peaks in the multiplicity and expected region. Because they were missing a group, all 1, 4-benzothiazines with a benzoyl group in their mass spectra had a peak at m/z = MM^+-105 (high intensity) and 105 ($CC_6C_6H£CO^+$ base peak). Peaks were seen at m/z = M+M+-C_2H_4, M+M+-C_2H_5, and MM+M+-OC_2H_5, or 2-ethoxycarbonyl derivatives.

DISCLOSURE STATEMENT:

There is no conflict of interest financial or otherwise.

ADDITIONAL INFORMATION

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