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Article

Synthesis, characterization and study of the biological activity of some new compounds containing Triazine and 1, 3, 4- Thiadiazol units

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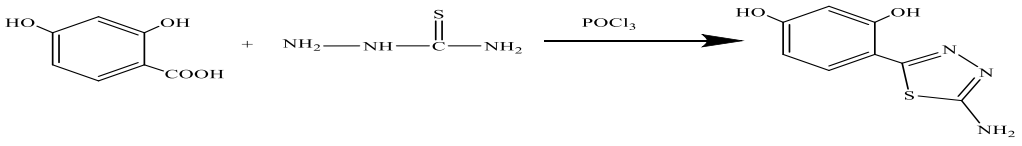
ABSTRACT
The work involves the synthesis of four new types from N-acetyl derivatives V_{a-d}, starting from 1,2,4-triazines. Carboxylic acid compound II (which was obtained from reacted compound I with α-chloroacetic acid in fused MeCOONa and ethanol) was treated with thiosemicarbazide in $POCl_3$ to give 1,3,4-thiadiazol compound III. Schiff bases resulted from the condensation of thiadiazole III with different benzaldehydes to form IV_{a-d}, which were converted to N-acetyl derivatives under an addition reaction with acetyl chloride. The antibacterial activity of newly synthesized compounds has been checked against *E.coli* gram (-), Klebsiella pneumoniae gram (-), and Staph. aureus gram (+) , and also on Strep .mutans gram (+). FTIR and ^{1}HNMR spectroscopy were used to characterize synthesized compounds.
Keywords: Triazine, 1,3,4-Thiadiazol, Schiff bases and N-acetyl compounds.

INTRODUCTION

1,2,4-Triazines are heterocyclic compounds (type six-membered ring) with general formula $C_3H_3N_3$. 1,2,4-Triazine derivatives have been found to indicate a wide variety of biological applications. [1,8] triazines were used as insecticides, dyes and herbicides [9]. Thiadiazole is a five–membered heterocyclic compound with diversified biological properties: anti-inflammatory, antifungal, antioxidant, antidepressant, and antitumoral agents. The derivatives of 1,3,4- thiadiazole were synthesized via many methods, such as in the literature [(10-12).] One of them includes reacted carboxylic acid with thiosemicarbazide in $POCl_3$ [13].



N-acyl derivatives could be obtained from the treated imines with acyl chloride in benzene. Tomma and co-workers [14,17] synthesized many N-acyl derivatives via an addition reaction of acetyl chloride on the imine group (dry benzene).

MATERIALS AND METHODS

Materials: The chemicals were supplied from Aldrich, GCC and Merck Chemicals Company.

Techniques: KBr discs record the FTIR on a Shimadzu (Ir prestige-21) FTIR spectroscopy. ^{1}HNMR was registered by the company Ultra Shield 300 MHz (Bruker, Switzerland). TMS was used as an internal standard with DMSO solvent. The TLC was done on (aluminum plates) coated with a layer of (Silica gel)using (n-hexane/ethyl acetate) (7:3).

Synthesis

In the following general procedure, Scheme 1 synthesized the new compounds.

Preparation of 1,2,4-triazine compound I was prepared according to the let [18].

Preparation of carboxylic acid II.

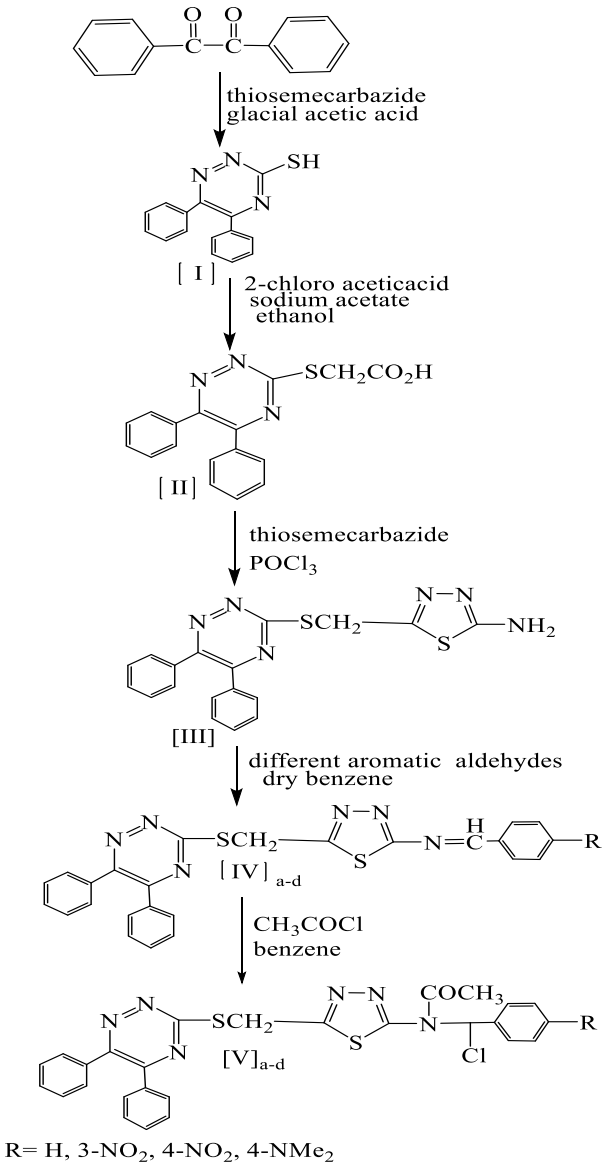
2-chloroacetic acid (0.094 mL, 0.001 mol) and sodium acetate fused (0.24g, 0.003 mol) were refluxed with compound [I] (0.256g, 0.001 mol) in ethanol for 6 hrs. After cooling, the mixture was poured onto cold water, filtered off the solid (yellow) [19,20], washed by the water, and dried. Recrystallization via using ethanol to get compound [II] yield 80 %, mp 98 -100 ^{0}C.

Synthesis of 1,3,4-thiadiazol-2-amine derivative III.

A mixture of thiosemicarbazide (0.91 g, 0.01 mol), acetic acid type II (0.3gm,0.01 mol) and $POCl_3$ (5mL) was heated for 24 hours. Then, cooling, the mixture was poured on crushed ice and neutralized by a concentrated sodium bicarbonate solution. The solid was filtered, washed with cold water, dried and recrystallized via ethanol. Yield 67%, m.p =190-192^{0}C; color: red [21].

Synthesis of imine compounds V_{a-d}.

In ethanol 3 mL, compound III(0.373g, 0.001 moles) was refluxed with an aldehyde (0.001 mol), using (four drops) from ACC for 8hrs[22]. The reaction was cooled, then crushed ice was used, the precipitate was filtered, and the solid was recrystallized from ethanol.



Scheme 1

Synthesis of N-acetyl derivatives V_{a-d}.

Acetyl chloride (0.02 mol.) was added dropwise to a stirred cool solution of compound IV (0.01mol.) in (10 mL) benzene. After that, the mixture was refluxed for (four hrs.). The reaction was cooled, poured into ice water, and then extracted from ethyl acetate to get a new N-acetyl product. The Physical data of the imine and N-acetyl compounds are recorded in Table 1.

RESULTS

The ring closure reaction of benzil with thiosemicarbazide in glacial acetic acid led to giving triazine compound, where this compound was reacted under nucleophilic reaction with α-chloroacetic acid in a basic medium to get carboxylic acid compound. This compound was identified via FTIR spectroscopy, which showed an absorption band at 1724 cm^{-1} due to (C=O), besides an absorption band at 3414 cm^{-1} due to νO-H of the carboxylic moiety. Also, the vanishment of ν(C=S) group with the release of νC-S at 717 cm^{-1}. 2-

Amino-1,3,4-thiadiazoles [III] were obtained from a ring closure reaction of the acid compound [II] with thiosemicarbazide in $POCl_3$. FTIR data of this compound[III] showed two peaks at 3385 cm^{-1} and 3250 cm^{-1} for stretching bands of NH_2 and a new peak at 1645 for the C=N bond. It also showed the disappearance of the characteristic bands of starting material[II], ^{1}HNMR spectrum (in DMSO) for compound III showed multiple signals between δ(7.36-7.50) ppm for ten protons (aromatic), two NH_2protons, and a signal type singlet at δ4,75 ppm for protons SCH_2.

Reaction equimolar from compound III and different aldehyde type aromatic led to obtained imine compound IV, identified by ^{1}HNMR and I.R. spectral data. The spectrum of ^{1}HNMR for compound IV_c showed a signal at δ 8.36 ppm due to protons of CH=N, many signals for aromatic protons at δ (7.15-7.87) ppm, singlet two signals at δ 4.23ppm and δ 2.09 ppm due to protons of SCH_2, $N(CH_3)_2$, respectively. While the ^{1}HNMR spectrum of compound IV_d showed a signal at δ 7.94 ppm for CH=N proton, many signals at δ (7.15-7.80) ppm (for aromatic protons), two protons of SCH_2 appeared at δ 4.23. Acetyl chloride was reacted with Schiff base $IV_{\mathbf{a-d}}$ in benzene (dry) to obtain N-acetyl compounds V_{a-d}; FTIR data confirmed these compounds via the vanishment of νC=N for Schiff bases and other peaks featured for the starting with the release of the band due to C=O and C-Cl in the region (1681-1662) $cm^{-1}$and(815-744) cm^{-1} respectively. The other I.R. data featured for compounds IV and V are recorded in Table 2. The ^{1}HNMR spectrum of compound V_b showed a number from signals at δ(7.46-7.96) ppm for protons (aromatic) and CH-Cl. Singlet two signals at δ 4.23ppm and δ 2.19ppm for SCH_2 and $COCH_3$ protons. The ^{1}HNMR of compound V_c showed a number from signals between δ(7.46-7.96) ppm for aromatic protons and CH-Cl. Singlet three signals at δ 4.23ppm, δ 2.17ppm, and δ 1.76ppm due to SCH_2, $COCH_3$ and $N(CH_3)_2$ protons, respectively.

Biological activity

Mutans (G+). Each of the compounds under test was dissolved in (DMSO as a control to give a concentration of 10^{-2}M). Millimeters were used to measure the inhibition zones. The antibacterial activities of the compound are listed in Table 3. This Table shows: First, schiff basses compounds IV_{a-c} showed no biological activity against E.coli (G-), Klebsiella pneumoniae (G-) and Staph. aureus (G+). While the Schiff base $[IV]_d$ showed only good antibacterial activity against E.coli (G-). Schiff bases IV_{a-c} showed good antibacterial activity against Strep .mutans (G+). Second, N-acetyl compounds V_{a-c} exhibited good antibacterial activity data against E.coli (G-) and (Klebsiella pneumoniae (G-) except V_a) but did not show any biological activity against Staph. aureus (G+) and Strep .mutans (G+).

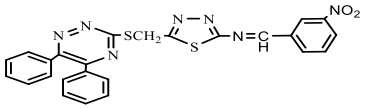
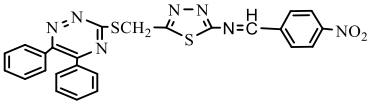
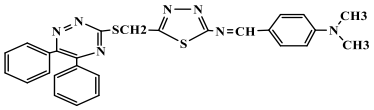
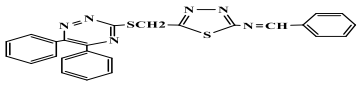
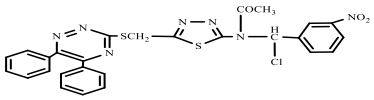
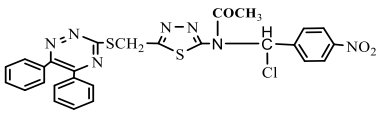
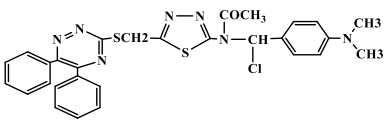
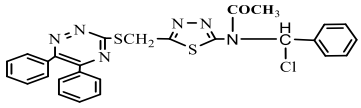
Comp. No.	Structural formula	Molecular formula	M.P°C	Yield%	Color
[IV]$_a$		$C_{25}H_{17}N_7O_2S_2$	138-140	61	Brown
[IV]$_b$		$C_{25}H_{17}N_7O_2S_2$	142-144	60	Brown
[IV]$_C$		$C_{27}H_{23}N_7S_2$	110-112	65	Brown
[IV]$_d$		$C_{25}H_{18}N_6S_2$	138-140	50	Brown
[V]$_a$		$C_{27}H_{20}ClN_7O_3S_2$	124-126	52	Brown
[V]$_b$		$C_{27}H_{20}ClN_7O_3S_2$	gummy	58	Brown
[V]$_c$		$C_{29}H_{26}ClN_7OS_2$	120-122	55	Brown
[V]$_d$		$C_{27}H_{21}ClN_6OS_2$	gummy	59	Brown

Table 1. The physical data of compounds IV$_{a-d}$, V$_{aud}$

Comp. No.	ν C-H arom.	νC-H ali-phatic	νC=Oa mid	νC=N exocyclic	νC=N endocyclic	νC=C aromatic	others
[IV]$_a$	3091	2924, 2856	-	1674	1628	1598	
[IV]$_b$	3059	2829, 2868	-	1678	1630	1595	**νNO2:1344,1519**
[IV]$_c$	3057	2937, 2868	-	1678	1631	1603	**νNO$_2$:1342,1522**
[IV]$_d$	3057	2933, 2868	-	1676	1630	1595	**νC-Me:1165**
[V]$_a$	3055	2929, 2865	1690	-	1618	1600	
[V]$_b$	3057	2937, 2868	1699	-	1607	1580	**νNO$_2$:1342,1520**
[V]$_c$	3050	2939, 2869	1694	-	1605	1582	**νNO$_2$:1342,1522**
[V]$_d$	**3055**	**2943, 2870**	**1684**	-	**1640**	**1597**	**νC-Me:1165**

Table 2: Absorption spectral data (FTIR, cm^{-1}) of compounds V$_{a-d}$ and VI$_{a-d}$.

Compound No.	Inhibition Zone (mm.)			
	E. Coli	*Klebsiella pneumoniae*	***Staph. aureus***	*Strep .mutans*
	Gram-negative(-)	**Gram-negative(-)**	**Gram (+)**	**Gram (+)**
[IV]$_a$	––	––	––	20
[IV]$_b$	––	––	––	20
[IV]$_c$	––	––	––	20
[IV]$_d$	18	––	––	––
[V]$_a$	18	––	––	––
[V]$_b$	10	10	––	––
[V]$_c$	20	20	––	––
Control(DMSO)	––		––	––

Table 3. Inhibition-Zones of Compounds IV$_{a-d}$ - VII $_{a-c}$

DISCUSSION

The ring closure reaction of benzil with thiosemicarbazide in glacial acetic acid [18] led to giving triazine compound, where this compound was reacted under nucleophilic reaction with α-chloroacetic acid in basic medium to get carboxylic acid compound.

FTIR absorption-spectra exhibited vanishment of the νNH_2 group together with the release of the band in the region (1678-1674) cm^{-1} is expected to imine $\nu(C=N)$ [23].

The antibacterial activity of IV_{a-d} and Va-c compounds was done according to the (agar diffusion method) [24], using Escherichia coli (G-), Klebsiella pneumoniae (G-), and Staph. aureus (G+) , and also on Strep.

CONCLUSION

It can be concluded that A reported synthesis and biological evaluation of new Schiff bases and their N-acetyl derivatives containing triazine and thiadiazole rings.

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