RESEARCH ARTICLE

Synthesis and Characterization of New Quinoline-2-ones Derived from Triazine Derivatives

Sahar F. Abbas[1*], Jumbad H. Tomma[2]

[1]*Department of Scientific Affairs, Al-Karkh University of Science, Baghdad, Iraq*
[2]*Department of Chemistry, College of Education for Pure Science, Ibn Al-Haitham, University of Baghdad, Baghdad, Iraq*

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ABSTRACT

The work involves the synthesis of new four types from quinolin-2-one derivatives [IV]a-d. starting with 5,6-diphenyl-1,2,4-triazine-3-thiol. Benzil was reacted with thiosemecarbazide in glical acetic acid to give compounds [I], which was reacted with chloroethyl acetate and fused sodium acetate in ethanol to get compound [II]. The condensation of ester[II] with hydrazine hydrate led to producing new acid hydrazide $[III]_a$ The reaction of acid hydrazide $[III]_a$ with coumarin compounds led to formation quinolin-2-one derivatives $[IV]_{a,b}$. On the other hand, hydrazine hydrate with ethanol were heated under reflux to produce a new hydrazineyl compound $[III]_b$ Then reaction $[III]_b$ with coumarin compounds led to the formation quinolin-2-one derivatives $[IV]_{c,d}$.

All newly synthesized compounds have been tested for their antibacterial activity against *Bacillus subtitis* gram (+)ve and *Escherichia coli* gram (-)ve bacteria and also on *Candida albicans* fungal, The synthesized compounds were characterized by melting points, FTIR, ^{1}HNMR, and Mass spectroscopy (of some of them).

Keywords: 1,2,4-Triazine, Hydrazineyl compound, Quinolin-2-one.

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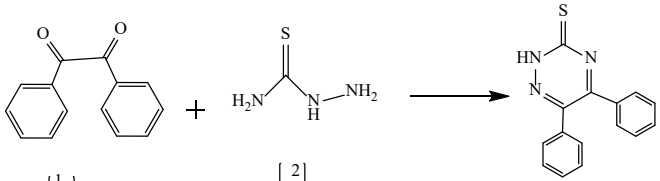
INTRODUCTION

1,2,4-Triazines are the six-membered heterocyclic compounds possessing three nitrogen in their structure with general formula $C_3H_3N_3$.

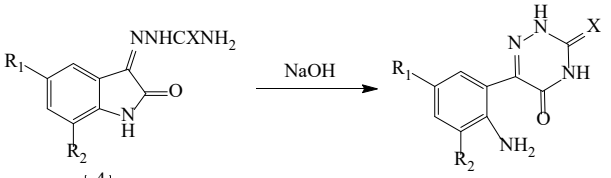
1,2,4-Triazines and its derivatives have been found to exhibit a variety of biological applications such as antifungal,[1] anti-HIV,[2] antiparasitic,[3] anticancer,[4] anti-inflammatory,[5] antiviral,[6] antimicrobial,[7] antimalarial.[8] Besides this, triazines were used as herbicides, pesticides, and dyes.[9]

The triazine derivatives synthesized by many methods were mentioned in the literature.[10-13] While Arshad. M *et al.*[14] synthesized the triazines as follows:



[1] [2] [3]

Kumar. R *et al.*[15] 6-(2-amino-3,5-substituted phenyl)-1,2,4 triazine derivatives[5] were synthesized by refluxing semicarbazones or thiosemicarbazones[4] in sodium hydroxide solution.



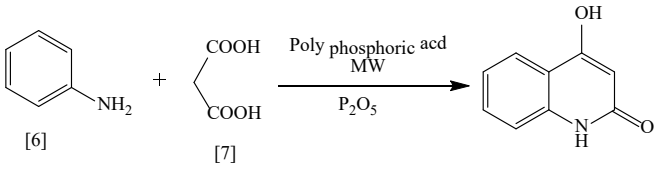
[4] [5]

X=O, S
R1=H, F, Cl, Br
R2=H, Br

Quinoline and its derivatives are important due to their wide range of biological activities as a drug analgesics, antiamoebic, tryphocidal, antiseptic, and anti-serotonin.[16-19] In addition to the quinolin, derivatives also exhibit good antimalarial, antitubercular, antibacterial, antihistaminic, anti-neurodegerative, anticonvulsant, antitumor, anticancers, and antiallergics activity.[6,20-22]

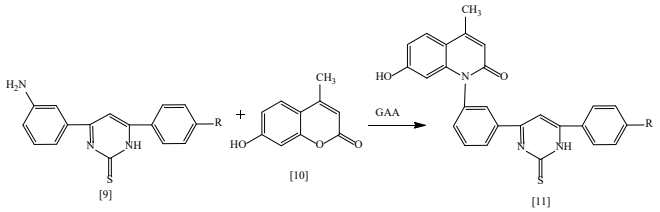
By using[23] another method and reagents, 4-hydroxyquinolin-2(1H)-one[8] was synthesized from the reaction of aniline[6] with malonic acid.[7] These compounds have antibacterial activity and antifungal activity

**Author for Correspondence: sahar.fadhil.2020@ kus. ed.iq*



[6] [7] [8]

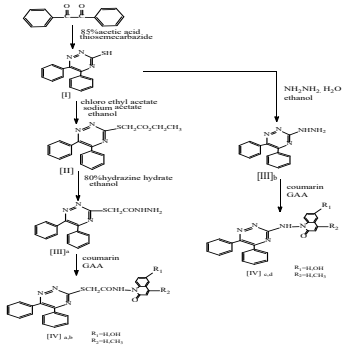
Tomma *et al*.,[23] were synthesized new quinolin -2-one dervitives[11] from condensation reaction of amino compounds[9] with coamarin[10] using glacial acetic as a catalyst and solvent.



[9] [10] [11]

R=4-Br , 4-NMe$_2$

The aim of this work is to syntheses of a new acid hydrazide derivatives is for 1,2,4-traizine and these derivative designs to be used for the synthesis of different new derivatives; quinolin-2-one



Scheme 1

MATERIALS AND METHODS

Materials

The chemicals were supplied from Merck, Fluka, GCC, and Aldrich chemicals Co.

Techniques: Using potassium bromide discs, the FTIR spectra were recorded on a Shimadzo (Ir prestige-21) FTIR spectroscopy. Uncorrected melting points were determined on Hot-Stage, Gallen Kamp melting point apparatus, ^{1}HNMR spectra were carried out by company: ultra shield 300 MHz, Bruker, Switzerland, at University of Kazi, Turkey, (TMS) was used as an internal standard with dimethylsulfoxide (DMSO) as a solvent. The TLC was performed on aluminum plates coated with layer of Silica gel, supplied by Merck, using (n-hexan/ethyl acetat) (7:3). The spots were detected by iodine vapor.

EXPERIMENTAL PROCEDURES

Synthesis of 5,6-diphenyl-1,2,4-triazine-3-thiol [I]

This compound was prepared according leterictuer[14] Benzil (1.05 g, 0.005 mol) was dissolved in 85% glacial acetic acid with thiosemecarbazide (0.455 g, 0.005 mol) in hot water (100 mL),the mixture was refluxed for 4 hours and the precipitate that appeared was filtered. The orange crystals obtained were recrystallized from ethanol to give orange solid, yield 87%, mp 222–224°C.

Synthesis of Ethyl 2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio) acetate [II]

Amixture of compound [I] (0.329 g,0.001 mol),[25] chloro ethyl acetate (0.122 mL, 0.001 mol) and fused sodium acetate (9.24 g, 0.003 mol) in ethanol was heated under reflux for 4 hours. Then cooled and poured onto water,the resulting yellow solid was filtered off, washed with water, dried, the recrystallization using ethanol to give compound [II], yield 80%, mp 98–100°C.

Synthesis of 2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio) acetohydrazide [III]$_a$. and 3-hydrazineyl-5,6-diphenyl-1,2,4-triazine [III]$_b$.

A solution of compound[II]a or compound [I]b (0.06 mol) and hydrazine hydrate (5 mL) in (10 mL) of ethanol was heated under reflux during 2 hours.[25] The mixture was then cooled to room temperature, and the solid obtained was filtered and recrystallized from ethanol.

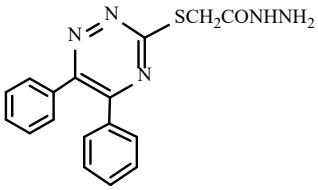
Synthesis of Quinolin-2-one derivatives [IV]$_{a-d}$

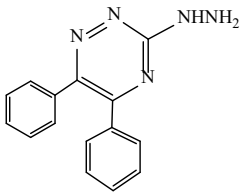
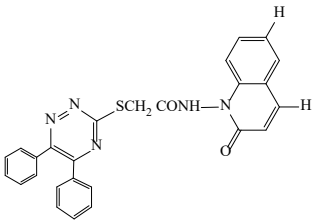
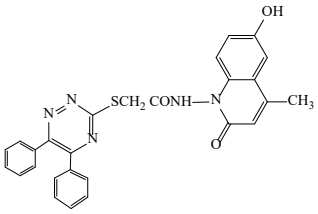
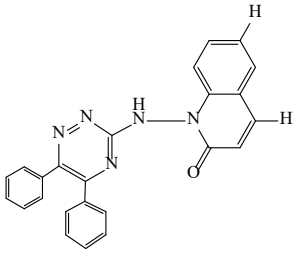
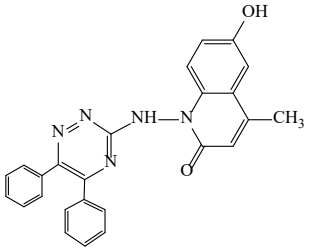
Equivalent moles of coumarin compounds (0.01 mol) and amine compounds[III]a, [III]b (0.01 mol) were dissolved in glacial acetic acid (3 mL) and refluxed for 6 hours[27] and the residue poured onto ice water to get a solid product. The obtained product was filtered, dried at room temperature, and recrystallized from acetone. The nomenclature, structural formula, yields, melting points, and color of the synthesized compounds [III]a,b -[IV]$_{a-d}$ were listed in Table 1.

RESULTS AND DISCUSSION

The trazine compound [I] was prepared from the reaction of equimolar of benzil and thiosmecarbazid in glacial acetic acid by the ring closure reaction.[14]

Table 1: The physical properties of compounds [III]a,b, [IV]a-d

Comp. no.	*Nomenclature*	*Structural formula*	*Matarial (°C)*	*Yield %*	*Color*
[II]$_a$	2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio) acetohydrazide		75–76	78	Brown

Comp. no.	*Nomenclature*	*Structural formula*	*Matarial (°C)*	*Yield %*	*Color*
$[III]_b$	3-hydrazineyl-5,6-diphenyl-1,2,4-triazine		178–180	80	Yellow
$[IV]_c$	1-(2-(5,6-diphenyl-1,2,4-triazine-3-sulfinimidoyl) acetyl)quinolin-2(1H)-one		198–200	87	Pale orang
$[IV]_d$	2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio) acetohydrazide		106–108	77	Dark brown
[IV]c	1-((5,6-diphenyl-1,2,4-triazin-3-yl) amino) quinolin-2(1H)-one		90–92	62	Pale orang
$[IV]_d$	1-((5,6-diphenyl-1,2,4-triazin-3-yl) amino)-6-hydroxy-4methylquinolin-2(1H)one		98–100	67	Dark brown

The structure of triazine [I] was characterized by Fourier Transform Infrared Spectroscopy (FTIR) spectrum. The FTIR spectrum showed the disappearance of absorption bands of (C=O) and (OH) groups and other peaks such as NH_2 groups of the starting materials together with the appearance of new absorption stretching bands due to C=S at (1190) cm^{-1}, N=N appeared at 1554 cm^{-1}, and the C=N stretching appeared at 1662 cm^{-1}.

The ester compounds [II] were characterized by FTIR spectroscopy. The FTIR spectrum, showed absorption bands at 1732 cm^{-1} and 1303 cm^{-1} due to stretching vibration of the (C=O) and (C-O) for the ester group, respectively, besides to the disappearance stretching band of(C=S) group with the appearance of stretching band for C-S at 717 cm^{-1}.

The condensation of ester [II] with hydrazine hydrate in ethanol led to the formation a corresponding acid hydrazide $[III]_a$. The compound $[III]_a$ was characterized by FTIR and ^{1}HNMR spectroscopy. The FTIR of compound [III]a showed new absorption bands at (3310–3180) cm^{-1} due to stretching a sym, and sym. of NH_2 and NH groups and stretching vibration band due to (C=O) of amide group (28) at 1631 cm^{-1} (Table 2).

^{1}HNMR spectrum (in DMSO as a solvent) of acid hydrazide $[III]_a$, showed a signal at (δ9.14) ppm due to of NH protons of hydrazide moiety. The spectrum also showed multiple signals in the region δ(7.21–7.45) ppm attributed to the ten aromatic protons, and a singlet signal at δ 5.3 ppm for two protons of NH_2 group besides to a singlet signal at δ4,0 ppm for SCH_2 protons. The structure of the compound $[III]_b$ was studied by FTIR and ^{1}HNMR spectroscopy. The FTIR spectrum, showed the disappearance of absorption band of the C=S with appearance

Table 2: Characteristic FTIR absorption bands data of quinline-2-one compounds $[IV]_{a-d}$

	Characteristic bands FTIR spectra (cm^{-1})							
Comp. no.	*υ (NH)*	*υ (C-H) aromatic*	*υ (C-H) aliphatic*	*υ (C=O)*	*υ (C=N)*	*υ (C=C)*	*υ C-N*	*Others*
$[IV]_a$	3417,3329	3008	2900-2873	1720,1678	1620	1602	1396	
$[IV]_b$	3211,3134	3055	2922-2850	1725,1668	1640	1602	1390	υ OH 3103
$[IV]_c$	3261-3157	3059	2927-2852	1620	1630	1600	1392	
$[IV]_d$	3200,3124	3060	2902-2850	1625	1640	1597	1390	OH 3220

Table 3: Inhibition zones of titled compounds ($[IV]_{a-d}$

	Inhibition zone (mm.)		
	B. subtilis	*E. coli*	*C. albicans*
Compound no.	*Gram positive(+)*	*Gram negative(-)*	*Gram negative(-)*
$[IV]_a$	18	20	—
[IV]b	20	18	—
[IV]c	20	26	21
[IV]d	20	22	25
Metroindazol	34	18	25
Control (DMSO)	—	—	—

new absorption stretching bands in the region 3325 to 3142 of NH_2 and NH groups (asym. and sym.) (Table 3).

The ^{1}HNMR spectrum (in DMSO-d_6 as a solvent) of compound $[III]_b$, showed a singlet signal at δ10.21 ppm could be attributed to a proton of NH group, many signals in the region δ(7.20–7.46) ppm for ten aromatic protons**.** Also, the spectrum showed a good signal at δ 6.15 ppm for two protons of NH_2 group.

The structure of quinoline derivatives $[IV]_{a-d}$ has been characterized by FTIR and ^{1}HNMR spectroscopy. Characteristic FTIR absorption bands of quinoline derivatives $[IV]_{a-d}$ showed a shifting data of in carbonyl stretching band C=O of lactam[29] group of quinoline-2-one then C=O of coumarin, and disappearance the two bands of NH_2 groups of acid hydrazide$[III]_a$ and compound $[III]_b$.

^{1}HNMR spectrum of compound $[IV]_c$, showed the following characteristic chemical shift (DMSO-d_6 as a solvent):a singlet signal at δ 11.89 ppm. This could be attributed for the proton of NH group. Many signals appeared in the region δ (6.93–7.88) ppm for aromatic protons. While appearance, a singlet signal at δ 6.52 ppm could be attributed to proton of C=CH of quinoline.

The mass spectrum of compound $[IV]_b$, showed the characteristic fragmentation[30] at m/z = 494 refers to the presence of molecular weight of the compound $[IV]_b$.

The mass spectrum of compound $[IV]_d$, showed the characteristic fragmentation at m/z = 421 refers to the presence of molecular weight of the compound $[IV]_d$.

CONCLUSIONS

In this work, new derivatives (esters, hydrazide, and their heterocyclic compounds) derived from 5,6-diphenyl-1,2,4-triazine-3-thiol were synthesized and characterized using a simple method the following conclusions could be drawn.

- Compound $[III]_a$ or compound $[III]_b$ was synthesized in ethanol in good yield, these compounds $[III]_a$, $[III]_b$ using as starting material for synthesized new quinolin-2-one derivatives $[IV]_{a-d}$ in moderate yield by simple method.
- The physical properties, spectral data give good information's of the suggested structure for the new synthesized compounds.
- Some compounds give good biological activity and other did not give any biological activities. That may be related to the functional groups and the chemical structure for the examined compounds.

REFERENCES

1. Hay MP, Pruijn FB, Gamage SA, Liyanage HS, Kovacs MS, Patterson AV, Wilson WR, Brown JM, Denny WA. DNA-targeted 1, 2, 4-benzotriazine 1, 4-dioxides: Potent analogues of the hypoxia-selective cytotoxin tirapazamine. Journal of medicinal chemistry. 2004 Jan 15;47(2):475-488.
2. Baliani A, Bueno GJ, Stewart ML, Yardley V, Brun R, Barrett MP, Gilbert IH. Design and synthesis of a series of melamine-based nitroheterocycles with activity against trypanosomatid parasites. Journal of Medicinal Chemistry. 2005 Aug 25;48(17):5570-5579.
3. Agarwal A, Srivastava K, Puri SK, Chauhan PM. Syntheses of 2, 4, 6-trisubstituted triazines as antimalarial agents. Bioorganic & medicinal chemistry letters. 2005 Feb 1;15(3):531-533.
4. Srinivas K, Srinivas U, Bhanuprakash K, Harakishore K, Murthy US, Rao VJ. Synthesis and antibacterial activity of various substituted s-triazines. European journal of medicinal chemistry. 2006 Nov 1;41(11):1240-1246.
5. Erickson JJ. The 1, 2, 4-Triazines. Chemistry of Heterocyclic Compounds: The 1, 2, 3-and 1, 2, 4-Triazines, Tetrazines & Pentazines. 1956; Jan 1, 10:44-137.
6. Hussein M, Kafafy AH, Abdel-Moty S, Abou-Ghadir O. Synthesis and biological activities of new substituted thiazoline-quinoline derivatives. Acta Pharmaceutica. 2009 Dec 1;59(4): 365.
7. El-Samii ZA. Synthesis and anti-inflammatory activity of some novel 1, 3, 4-oxadiazole derivatives. Journal of Chemical Technology & Biotechnology. 1992;53(2):143-146.
8. Partridge MW, Stevens MF. Pyrazolo-as-triazines. Part I. Journal of the Chemical Society C: Organic. 1966:1127-1131.
9. Abdel-Rahman RM, Morsy JM, Hanafy F, Amene HA, Synthesis of heterobicyclic nitrogen systems bearing the 1,2,4-triazine moiety as anti-HIV and anticancer drugs: Part I. Pharmazie, 1999;54(5):347-351.

10. Phucho T, Nongpiur A, Tumtin S, Nongrum R, Myrboh B, Nonghlaw RL. Novel one pot synthesis of substituted 1, 2, 4-triazines. Arkivoc. 2008 Jan 1;15:79-87.
11. Azizian J, Krimi AR, "Synthesis of Trisubstituted 1,2,4-Triazine in Presence of $NaHSO_4/SiO_2$'' Asian Journal of Chemistry, 2010;23(3):980-982.
12. Patel D, Toliwal SD, Patel JV, Jadav K, Gupte A, Patel Y. Studies on microwave assisted synthesis of triazines from byproducts of oil processing industries. Journal of Applied Chemical Research, 2011;16:53-60.
13. Horner K, Valette N, Web M, "Strain-promoted reaction of 1,2, 4-triazines with bicyclononynes",Chemistry –Aeuropean journal, 2015;21(41):14376-14381.
14. Arshad M, Bibi A, Mahmood T, Asiri A, Ayub K, "Synthesis, Crystal Structures and Spectroscopic Properties ofTriazine-Based Hydrazone Derivatives; A Comparative Experimental-Theoretical Study", Molecules, 2015;20:5851-5874.
15. Kumar R, Roy RK, Singh A. 6 (3, 5-Substituted-2-bromo phenyl) 1, 2, 4-triazine derivatives as antimicrobial and anticancer agents. World J. Pharm. Pharmaceut. Sci. 2018;7:1316-1324.
16. Kumar RN, Suresh T, Mohan PS. Isolation of 4-chloro-3-formyl-2-(2-hydroxyethene-1-yl) quinolines by Vilsmeier Haack reaction on quinaldines: Construction of diazepino quinoline heterocycles and their antimicrobial and cytogenetic studies. Acta Pharmaceutica-Zagreb. 2003 Mar 1;53(1):1-4.
17. Quan A, Wang J, Rho J, Kwak K, Kang H, Jun C, Cha K, Bull. Korean. Chem. Soc., 2005;26(11):1757-1760.
18. Özyanik M, Demirci S, Bektaş H, Demirbaş N, Demirbaş A, Karaoğlu ŞA. Preparation and antimicrobial activity evaluation of some quinoline derivatives containing an azole nucleus. Turkish Journal of Chemistry. 2012 Apr 11;36(2):233-246.
19. Denmark SE, Venkatraman S. On the mechanism of the Skraup– Doebner– Von Miller quinoline synthesis. The Journal of organic chemistry. 2006 Feb 17;71(4):1668-1676.
20. Charris JE, Lobo GM, Camacho J, Ferrer R, Barazarte A, Dominguez JN, Gamboa N, Rodrigues JR, Angel JE. Synthesis and antimalarial activity of (E) 2-(2'-chloro-3'-quinolinylmethylidene)-5, 7-dimethoxyindanones. Letters in Drug Design & Discovery. 2007 Jan 1;4(1):49-54.
21. Chen YL, Hung HM, Lu CM, Li KC, Tzeng CC. Synthesis and anticancer evaluation of certain indolo [2, 3-b] quinoline derivatives. Bioorganic & medicinal chemistry. 2004 Dec 15;12(24):6539-6546.
22. Prajapati SM, Vekariya RH, Patel KD, Panchal SN, Patel HD, Rajani DP, Rajani S. Synthesis and in vitro antibacterial and antifungal evaluation of quinoline analogue azetidin and thiazolidin derivatives. International Letters of Chemistry, Physics and Astronomy. 2014;20.
23. Tomma JH, Hussein DF, Jamel NM. Synthesis and Characterization of Some New Quinoline-2-one, Schiff bases, Pyrazole and Pyrazoline Compounds Derived From Hydrazide Containing Isoxazoline or Pyrimidine Cycles. Iraqi Journal of Science. 2016;57(2C):1316-1332.
24. Jamel NM, Hussein DF, Tomma JH. Synthesis and Characterization New Schiff Bases, Pyrazole and Pyrazoline Compounds Derived From Acid Hydrazide Containing Isoxazoline Ring. Ibn AL-Haitham Journal For Pure and Applied Science. 2017 Apr 12; 27(3):435-447.
25. Karam NH, Tomi IH, Tomma JH. Synthesis, Characterization and Study of The Liquid Crystalline Behavior of Four and Six Heterocyclic Compounds. Iraqi Journal of Science. 2016;57(3B):1876-1890.
26. Jamel NM, "Synthesis and Characterization of NewHeterocyclic Compounds Derived from Chalcones", M.Sc.Thesis, College of Education For Pure Science Ibn-Al-Haitham, University. of Baghdad (2014).
27. Abbas SF, Tomma JH, Ali ET. Synthesis And Characterization Of New Schiff Bases And Their 1, 3-Oxazepines Derived From Phthalic Anhydride. Systematic Reviews in Pharmacy. 2021;12(2):260-265.
28. Sharma YR. Organic spectroscopy. S. Chand and Company Ltd. 2010;5:112.
29. Porter N,"Mass spectroscopy of heterocyclic compounds", 2nd ed, John Wiley Sons, New York (1984).