Egypt. J. Chem. **Vol. 65**, No. 11 pp. 305 - 312 (2022)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis & Biological Evaluation of Novel Series of Benzo[f]indazole Derivatives

Ahmed M. Hamdoon[1], Mohanad Y. Saleh[2,*], Shakir Mahmood Saied[3]

[1] *Branch of Basic Science, College of Agriculture and Forestry, University of Mosul.*

[2] *Department of Chemistry, College of Education for pure Science, University of Mosul.*

[3] *Department of Medical Laboratories Technologies Al-Noor University College, Barttella, Iraq .*

Abstract

A new series of benzo[f]indazole derivatives was synthesized via cyclo-condensation of β-ketoester with arylidenes derivatives in the presence of alcoholic sodium hydroxide to afford octahydronaphthalene-2-carboxylates. 1,3-Dipolar cycloaddition between these carboxylates and hydrazine hydrate to form benzo[f]indazole derivatives. New obtained compounds were characterized upon elemental and spectroscopic analyses. Antibacterial activity of selected derivatives was evaluated.

Keyword: Benzo[f]indazole, Biological Evaluation, Chalgone, β- keto ester

1. Introduction

Indazole derivatives scarcely occur in nature, but this particular nucleus in a variety of synthetic compounds possesses a wide range of pharmacological activities, such as anti-inflammatory, antiarrhythmic, antitumor, antifungal, antibacterial, and anti-HIV activities.[1-7]

Diversely substituted indazole-containing compounds furnished with different functional groups represent significant pharmacological activities and serve as structural motifs in drug molecules. For example, niraparib **1** (Figure 1) has been widely used as an anticancer drug for the treatment of recurrent epithelial ovarian, fallopian tube or primary peritoneal, breast and prostate cancer [8]. Pazopanib **2** (Figure 1) is a tyrosine kinase inhibitor, which has been approved by the FDA for renal cell carcinoma [9, 10]. Bendazac **3** and Benzydamine **4** are two commercially available anti-inflammatory drugs, which contain the 1H-indazole scaffold.[11, 12]

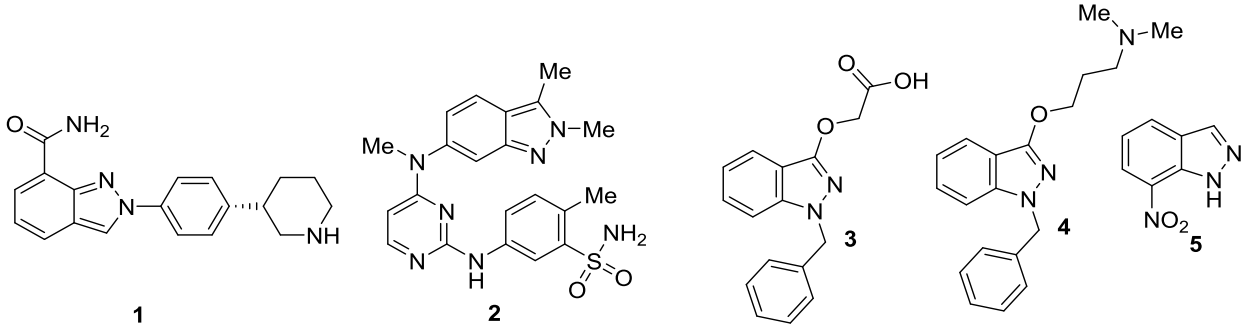


Figure 1: Chemical structure of indazole-containing drugs **1**–**5**.[2]

The famous indazole derivative was 7-nitroindazole (7NI, **5**), which was a nerve harm preventer by dropping the oxidative stress or via reducing the peroxynitrite formed in the nerve tissues and inhibited the enzyme type 1 nitric oxide synthase and produced an anticonvulsive activities (Figure 1) [13].

*Corresponding author e-mail: mohanadalallaf@uomosul.edu.iq; (Mohanad Y. Saleh).

Receive Date: 08 February 2022; Revise Date: 03 March 2022; Accept Date: 06 March 2022.

DOI: 10.21608/EJCHEM.2022.120818.5418.

Benzo[f]indazole nucleus was the bases of several biological activities [14]The introducing of dimethyl groups on the position 6 of this moiety may increase hopefully the steric effects of these tricyclic compound and thereby, protect this cyclohexanone ring from degradation in the same way as has been suggested for analogues rings, and it was also relatively increased resistant to acid hydrolysis and, therefore, may be administered orally with good effect [15].

In light of indazole scaffolds exhibiting a broad spectrum of pharmacological activities, numerous methods have been developed to construct of these heterocycles with better biological activities. So, The aim of our work is synthesis characterization, and antimicrobial evaluation of novel series of benzo[f]indazole derivatives.

2. Experimental

2.1. General

Melting points were verified using the electrothermal 9300 (U.K) and uncorrected. **UV** spectra were measured by Shimadzu, UV-160, UV /Visible Recording Spectrophotometer. **FTIR** were determined on Tensor 27 Co. Brucker, 2003, Germany as either (KBr) disc or films. **NMR** spectra were recorded on a Bruker (300 MHz) in Al-Albayt University/ Jordon, using TMS as an internal standard in DMSO/$CDCl_3$ as a solvent.

2.2. Synthesis of 2-Arylidene-5,5-dimethylcyclohexane-1,3-dione 7a-e

Compounds **7a-e** were prepared as mentioned by literature [16]. equimolecular appropriate chalcones analogous **6a-e** and ethyl acetoacetate with 20ml alcoholic sodium hydroxide solution (added dropwise) at room temperature with continuous string. This mixture was refluxed for 4h (TLC), cooled and the precipitated product was filtered and washed with water and recrystallized from a mixture of ethanol-cyclohexane to afford **7a-e**.

2.3. 4-Aryl-7,7-dimethyl-2,4,4a,6,7,8-hexahydro-3H-benzo[f]indazole-3,5(3aH)-diones 8a-e:

Hydrazine hydrate (80%) (1mmoles) was added dropwise with stirring to a solution of appropriate carboxylate **7a-e** in 30 mL absolute ethanol[17]. The reaction mixture was refluxed for 6-8h (TLC) then lifted overnight to afford a precipitate which was filtrated, washed with water and recrystallized from ethanol to compounds **8a-e**. Melting points, yield and UV of these new compounds were shown in Table 1, while the FTIR were shown in Table 2.

Table 1: Melting points, % yields and u.v. spectra of compounds 7a-e and 8a-e

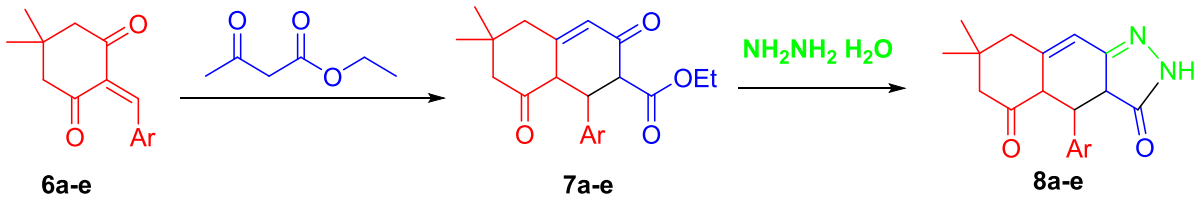
	M.p.ºC	Yield %	λ_{max}(nm)		M.p.ºC	Yield %	λ_{max}(nm)
7a	202-204	62	310	**8a**	178-180	53	254
7b	164-166	71	319	**8b**	225-227	60	242
7c	193-195	44	326	**8c**	158-160	51	288
7d	148-150	55	304	**8d**	202-204	64	248
7e	211-213	76	300	**8e**	255 (decomposed)	69	261

Table (2): FTIR Spectra of compounds 7a-e and 8a-e

	IR, KBr , γ (cm^{-1})						
	Ester C=O	Cyclohexanone C=O	ester C-C-O		amide C=O	C=N Pyrazolone	NH pyrazolone
7a	1718.60	1736.44	1238,1115	**8a**	1735.44	1687 1529	3395.48
7b	1716	1735	1233,1130	**8b**	1730	1687 1525	3393
7c	1711	1735	1235, 1167	**8c**	1733	1680 1520	3391
7d	1711	1736	1235,1110	**8d**	1735	1686 1522	3392
7e	1718	1730	1238,1067	**8e**	1722	1680 1522	3389

3. Results and Discussion

2-Arylidene-5,5-dimethylcyclohexane-1,3-dione **6a-e** reacted with ethyl acetoacetate in the presence of alcoholic sodium ethoxide at reflux temperature to afford derivatives of ethyl 6,6-dimethyl-3,8-dioxo-1-arylidine-1,2,3,5,6,7,8,8a-octahydronaphthalene-2-carboxylate **7a-e** in excellent yield (Scheme 1).



Scheme 1

In the same manner, derivatives of 7,7-dimethyl-4-aryl-2,4,4a,6,7,8-hexahydro-3H-benzo[f]indazole-3,5(3aH)-dione **8a-e** were prepared via reaction of compounds 7a-e with hydrazine hydrate in absolute ethanol at reflux temperature (Scheme 1)[18]. The structures of new compounds **7a-e** and **8a-e** were proved upon elemental and spectroscopic data of NMR, UV, and FTIR spectra.

3.1. ^{1}H NMR Spectroscopic study:

^{1}H NMR spectra of compounds **7a-e** exhibited a single peak at δ 1.0-1.4 ppm which was assigned for two methyl groups, two single peaks at δ 1.70 and 1.95 ppm of protons at carbon (8), two peaks at δ 2.19 and 2.44 ppm CH carbon (6) of the same ring. benzo[f]indazole ring exhibited two single peaks at δ 3.30 and 3.32 ppm for the two protons at carbons 4 and 4a respectively, vinylic proton at carbon (9) was exhibited one single peak appeared at δ 5.97ppm and one peak at δ 2.7 ppm was assigned for carbon (4a) proton, a single peak at δ 3.72 ppm was assigned for methoxy group and. Finally, multiple peaks at δ 6.90-7.52 ppm were assigned to aromatic protons while a single peak at δ 12.34ppm was assigned to –NH (Figure 2)[19].

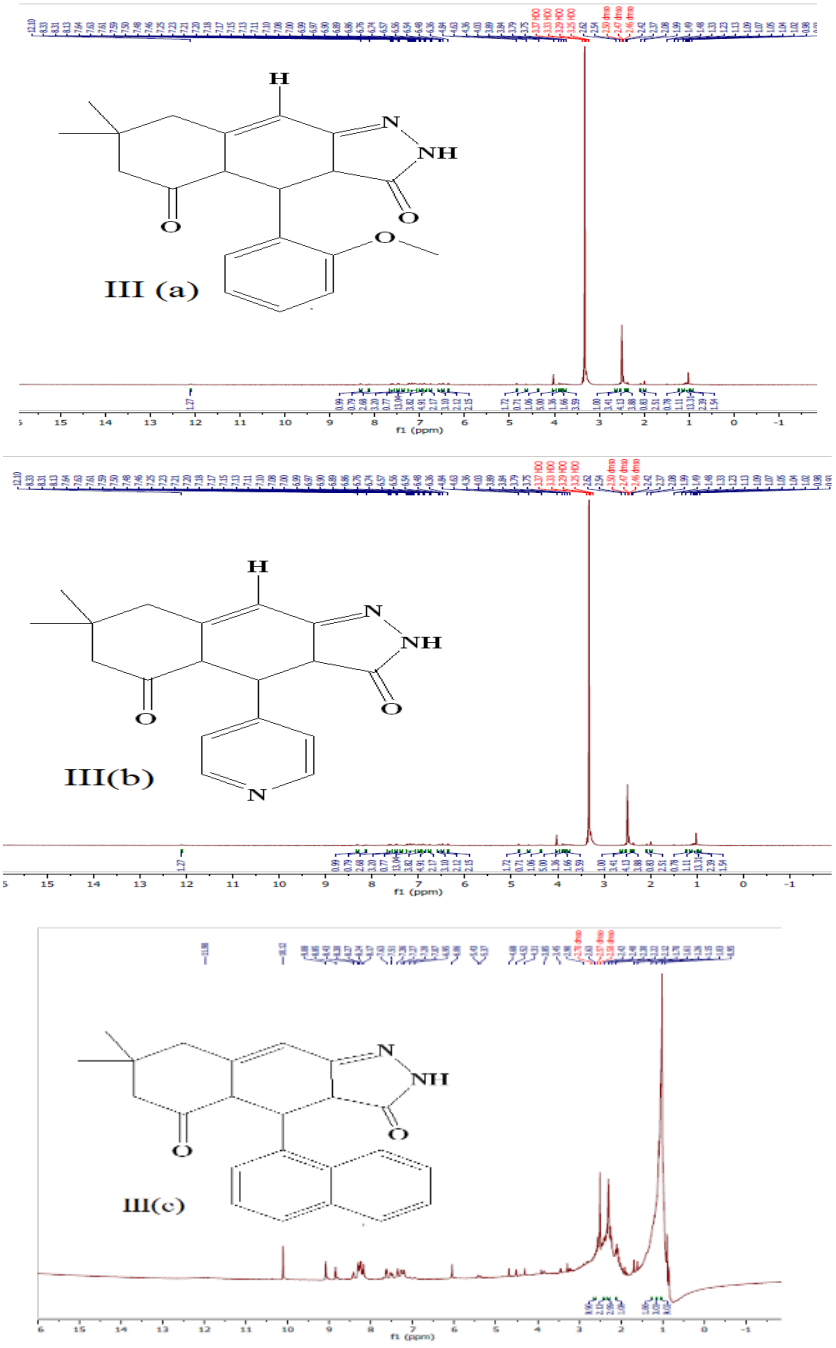


Figure 2: Selected NMR spectra of compounds 7a-e

3.2. The U.V. Spectroscopic study:

The max(nm) in $CHCl_3$ of all coloured beta keto esters derivatives **7a-e** were 300-326, Table (1) and this were due to their α,β – unsaturated carbonyl cyclic system of extensively conjugated pi-electrons. The highest absorption was 326 max(nm) in $CHCl_3$ of theses β-keto esters compounds **8a-e** were 300-326, (Figure 3). The energetically most favourable $\pi - \pi^*$ excitation occurs from the highest energy bonding pi-orbital (HOMO) to the lowest energy antibonding pi-orbital (LUMO).This clearly proved the importance of chromophore conjugation which shifted the absorption maximum to longer wavelengths and also demonstrated that each additional double bond in the conjugated pi-electron system increased the absorption maximum shifts

about 39 nm in the same direction which commonly results in bathochromic (shift to red), this shift was also result from the addition of conjugation in naphthalene group at position 4. All these factors in addition to keto-enol tautomerism in these beta keto esters increased the stability of these structures and thus increased shift to red[20].

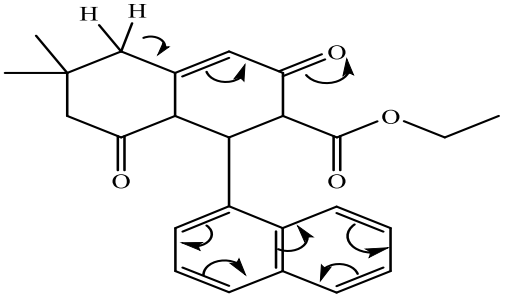


Figure 2: Binaphthalene-2-carboxylate derivative 7c of the highest absorption was 326 max(nm) in $CHCl_3$ of the all coloured beta keto esters compounds 7a-e

UV of compounds **8a-e** were 242-288, this was due to the two absorption bands in the near UV, these longest wavelength absorptions (up to 288nm) were due to the $\pi - \pi^*$ transitions of the conjugation and keto-enol tautomerism which increased the force constant and thus increased the stability of molecule which was the cause of longer wavelength (lower frequency) of UV spectra of these compounds. Besides, this bathochromic shift of UV absorption spectra was the substitution in the 4 and 5 positions (the fusing of pyrazole ring) which led to a much larger bathochromic shift (> 10 nm) (Table 1). The ketone form was predominated due to many factors that affected this form like the polarity of $CHCl_3$ solvent, high temperature, neutral pH and electron withdrawing substituents, [4], (Figure 3)[21].

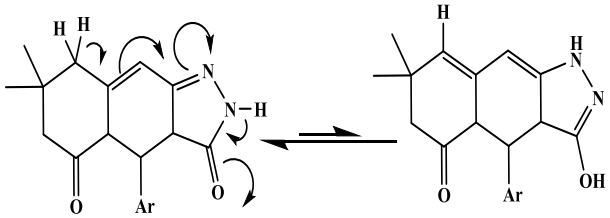


Figure 3

3.3. FT-IR Spectroscopic study:

The FT-IR spectra of compounds **7a-e** revealed absorption peaks at 1730-1736.55cm^{-1} (C=O) cyclohexanone, 1711-1718.60 cm^{-1} (C=O) ester and 1235-1238.44 cm^{-1} (Adamantane C-H) and 1495-1633 cm-1 (C-C-O) ester,(Figure 4, Table 2). Also, FTIR of The FT-IR spectra of compounds **8a-e** showed significant characteristic absorption two peaks at 1322-1329 cm^{-1} and 1380-1387cm^{-1}(C=N) pyrazolone, 1735.44-1722cm^{-1} (C=O) cyclic amide and finally, 3395-3389 cm^{-1} (NH) pyrazolone, The infrared values are in agreement with what was obtained from previous literature[22-24] Table (2).

3.4. Antimicrobial Study

New synthesized compounds **7a-e** and **8a-e** were evaluated *in vitro* for their antibacterial activity against *S. aureus*, *S. epidermidis*, *E. coli* and *Proteus Vulgar* using filter paper disk diffusion method [25-29]at a concentration of (100 mg / ml) in dimethyl sulfoxide as a solvent was the procedure used in this evaluated procedure.

As shown in Table (3), only compound **7e** showed activity against all of the tested microorganisms except *S. epidermidis.*Meanwhile, only compounds **8c,e** displayed inhibitory activity against all of the tested microorganisms equally or slightly more than the ciprofloxacin which was used as a reference. The all remain compounds **8** were practically inactive against the tested microorganisms.

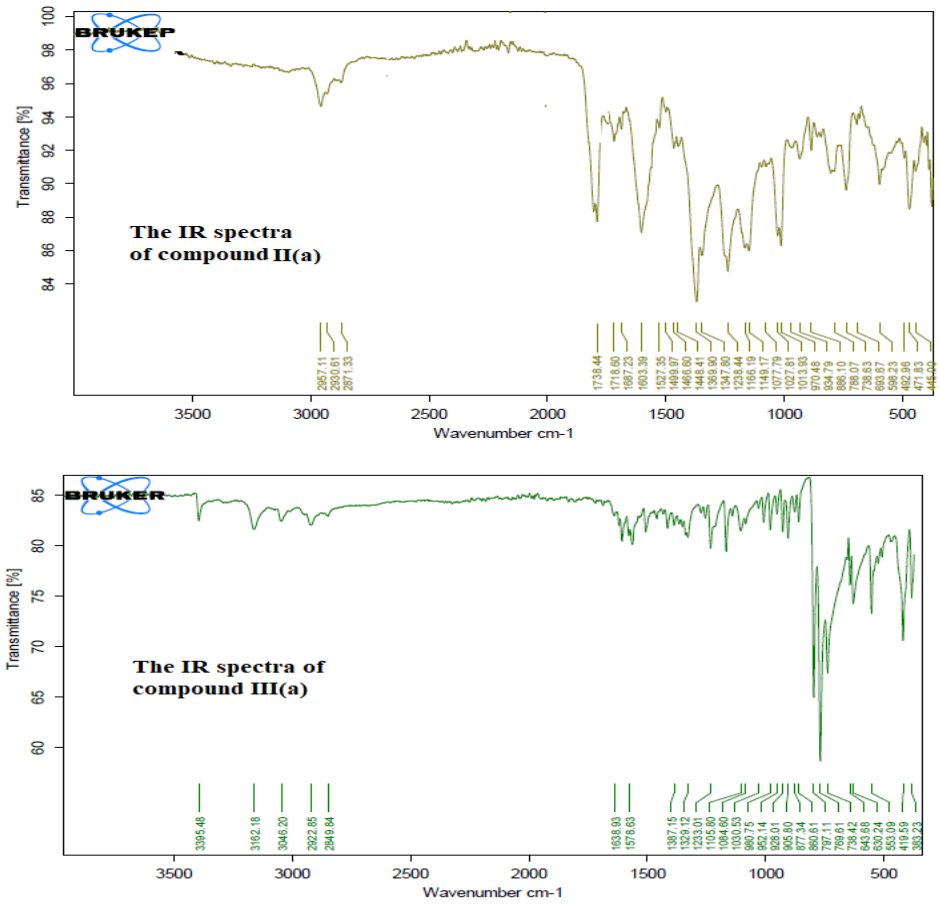


Figure 4: FT-IR Spectra of compounds 7a and 8a

Table (3): Antibacterial evaluation of new compounds I(a-e) and II (a-e)

Compound	Zone of inhibition in mm			
	S. aureus 10 mg / disk	*S. epidermidis* 10 mg / disk	*E. coli* 10 mg / disk	*Proteus Vulgar* 10 mg / disk
7a	8	8	6	8
7b	12	7	7	10
7c	11	12	12	8
7d	15	16	17	22
7e	28	27	28	29
8a	25	21	19	19
8b	18	22	21	19
8c	27	31	24	25
8d	22	25	21	27
8e	28	31	27	27
Control	26	28	24	25

4. Conclusions

It was concluded that simple procedure cyclocondensation of arylidenes derivatives with β-ketoester ethyl acetoacetate, (EAA) in the presence of alcoholic sodium hydroxide yielded ethyl 6,6-dimethyl-3,8-dioxo-1-aryl-1,2,3,5,6,7,8,8a -octahydronaphthalene-2-carboxylates **7a-e** of yield between (44-76 %). Also, these carboxylates were reacted with hydrazine hydrate via a simple and efficient 1,3-dipolar cycloaddition to form the title benzo[f]indazole derivatives **8a-e** with 51-69% yield.with antimicrobial activity of some compounds.

5. Acknowledgements

The authors are grateful to University of Mosul and Al-Noor University College Bartella Iraq for their financial support and providing facilities that made this work possible.

6. References

[1] F.C. Teixeira, H. Ramos, I.F. Antunes, M.J.M. Curto, M.T. Duarte, I. Bento, Synthesis and structural characterization of 1-and 2-substituted indazoles: ester and carboxylic acid derivatives, Molecules 11(11) (2006) 867-889.

[2] S.-G. Zhang, C.-G. Liang, W.-H. Zhang, Recent advances in indazole-containing derivatives: synthesis and biological perspectives, Molecules 23(11) (2018) 2783.

[3] S. Vidyacharan, A. Murugan, D.S. Sharada, C (sp 2)–H functionalization of 2 H-indazoles at C3-position via palladium (II)-catalyzed isocyanide insertion strategy leading to diverse heterocycles, The Journal of Organic Chemistry 81(7) (2016) 2837-2848.

[4] Saied, S., Saleh, M., Hamdoon, A. (2022). Multicomponent Synthesis of Tetrahydrobenzo[a]xanthene and Tetrahydrobenzo[a]acridine Derivatives using Sulfonated Multi-Walled Carbon Nanotubes as Heterogeneous Nanocatalysts. *Iranian Journal of Catalysis*, 12(2), 189-205. doi: 10.30495/ijc.2022.1955651.1924

[5] S. Behrouz, Highly Efficient One- Pot Three Component Synthesis of 2H- Indazoles by Consecutive Condensation, C–N and N–N Bond Formations Using Cu/Aminoclay/Reduced Graphene Oxide Nanohybrid, Journal of Heterocyclic Chemistry 54(3) (2017) 1863-1871.

[6] M. Jayanthi, P. Rajakumar, Synthesis, cell viability, and flow cytometric fluorescence pulse width analysis of dendrimers with indazoles surface unit, Journal of Heterocyclic Chemistry 54(6) (2017) 3042-3050.

[7] Saeed, Z., Saleh, M., sadeek, G. (2022). Synthesis and Biological Evolution of Novel Substituted 1,2,4-triazine from Sulfanilic Acid. *Egyptian Journal of Chemistry*, (), -. doi: 10.21608/ejchem.2022.132916.5870

[8] L.J. Scott, Niraparib: first global approval, Drugs 77(9) (2017) 1029-1034.

[9] S.R. Baddam, N.U. Kumar, A.P. Reddy, R. Bandichhor, Regioselective methylation of indazoles using methyl 2, 2, 2-trichloromethylacetimidate, Tetrahedron Letters 54(13) (2013) 1661-1663.

[10] L.S. Boulos, M.H.N. Arsanious, E.F. Ewies, F. Ramzy, Reactions of 5(4H)-oxazolones with Wittig-Horner reagents: Novel synthesis of dioxopyrrolidinephosphonates and phosphonoalkanoates with anticipated schistosomicidal activity, Z. Naturforsch. Sect. B J. Chem. Sci. 63(10) (2008) 1211-1218.

[11] A.S. Al-Bogami, Mechanochemical synthesis of cyclohexenones and indazoles as potential antimicrobial agents, Research on Chemical Intermediates 42(6) (2016) 5457-5477.

[12] R.S. Gouhar, E.F. Ewies, M.F. El-Shehry, M.N.F. Shaheen, E.M.M.E. Ibrahim, Synthesis and Utility of α,β-Unsaturated Ketone Bearing Naphthalene and Benzofuran Rings in the Synthesis of Some N-heterocycles with Their Antiviral and Antitumor Activity Evaluation, Journal of Heterocyclic Chemistry 55(10) (2018) 2368-2380.

[13] P. Moore, P. Wallace, Z. Gaffen, S. Hart, R. Babbedge, Characterization of the novel nitric oxide synthase inhibitor 7- nitro indazole and related indazoles: antinociceptive and cardiovascular effects, British journal of pharmacology 110(1) (1993) 219-224.

[14] X. Wu, S. Wang, C. Liu, C. Zhang, J. Guo, X. Shang, A new 2H-benzindazole compound from Alternaria alternata Shm-1, an endophytic fungus isolated from the fresh wild fruit of Phellinus igniarius, Journal of natural medicines 73(3) (2019) 620-626.

[15] J.N. Delgado, Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry, Lippincott1991.

[16] Y. Budak, E. Findik, M. Ceylan, Cyclohexenones Through Addition of Ethyl Acetoacetate to 3-Aryl-1-(thiophen-3-yl) prop-2-en-1-one Derivatives, South African Journal of Chemistry 63 (2010) 1-5.

[17] Hamdoon, A. M., Al-Iraqi, M. A., & Saleh, M. Y. (2022). Synthesis of Some Multi-cyclic Sulfhydryl

Donor Compounds Containing 1, 2-dithiol-3-thione moiety. Egyptian Journal of Chemistry, 65(3), 1-2.
[18] Sdeek, G. T., Mauf, R. M., & Saleh, M. Y. (2021). Synthesis and Identification of some new Derivatives Oxazole, Thiazole and Imidazol from Acetyl Cysteine. Egyptian Journal of Chemistry, 64(12), 7565-7571.
[19] Ayoob, A., Sadeek, G., Saleh, M. (2022). Synthesis and Biologically Activity of Novel 2-Chloro -3-Formyl -1,5-Naphthyridine Chalcone Derivatives. *Journal of Chemical Health Risks*, 12(1), 73-79. doi: 10.22034/jchr.2022.688560
[20] Al-Thakafy, N. T., Al-Enizzi, M. S., & Saleh, M. Y. (2021). Synthesis of new Organic reagent by Vilsmeier–Haack reaction and estimation of pharmaceutical compounds (Mesalazine) containing aromatic amine groups. Egyptian Journal of Chemistry.
[21] Mohammed, E. R., Saied, S. M., & Saleh, M. Y. (2021). Synthesis, Characterization and Biological Evaluation Study of Cephalexin (Ceph) and Isatin Schiff base and Its Complexation with Some Divalent Metal Ions. Egyptian Journal of Chemistry.
[22] Saleh, M., Ayoub, A. I., & Hammady, A. O. (2020). Synthesis biological studies of some new heterocyclic compound derived from 2-chloro-3-formyl quinoline and 4-(benzyl sulfonyl) acetophenone. Egyptian Journal of Chemistry, 63(12), 4769-4776.
[23] Abbas, A. M., Mohammed Taib, A. S., & Saeed, N. H. (2020). Synthesis and Characterization of Linear Thermally Stable polyester contain Schiff Bases. Egyptian Journal of Chemistry, 63(8), 2999-3013.
[24] Saied, S., Mohammed, S., Khaleel, B., Saleh, M. (2021). Comparative Studies between Conventional Techniques and Green Chemistry to Synthesis of Novel Piperidinium Salts Ionic Liquids (PBSILs). *Journal of Chemical Health Risks*, 11(4), 451-456. doi: 10.22034/jchr.2021.686640
[25] D. Raahave, Paper disk-agar diffusion assay of penicillin in the presence of streptomycin, Antimicrobial Agents and Chemotherapy 6(5) (1974) 603-605.
[26] M.A. Abid, L. Latif, D.A. Kadhim, W.J. Aziz, Antimicrobial activity by diffusion method using iron oxide nanoparticles prepared from (Rose plant) extract with rust iron, Journal of Physics: Conference Series, IOP Publishing, 2021, p. 032068.
[27] H.M. Ibrahim, A.A. Aly, G.M. Taha, H.I. Ibrahim, Production of antibacterial cotton fabrics via green treatment with nontoxic natural biopolymer gelatin, egyptian Journal of Chemistry 62(Special Issue (Part 2) Innovation in Chemistry) (2019) 655-669.
[28] A.S. Hassan, G. O Moustafa, N.M. Morsy, A.M. Abdou, T.S. Hafez, Design, synthesis and antibacterial activity of N-aryl-3-(arylamino)-5-(((5-substituted furan-2-yl) methylene) amino)-1H-pyrazole-4-carboxamide as Nitrofurantoin® analogues, Egyptian Journal of Chemistry 63(11) (2020) 4469-4481.
[29] E.F. Ewies, M. El- Hussieny, N.F. El- Sayed, M. El- Shazly, Y.C. Chen, Y.C. Liu, Preparation of novel azidopyrazole derivatives with anticipated cytotoxic and antimicrobial activities, Journal of Heterocyclic Chemistry 57(3) (2020) 965-977.