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Multicomponent approach to the synthesis and spectral characterization of some 3,5-pyrazolididione derivatives and evaluation as anti-inflammatory agents

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A B S T R A C T

Pyrazolones are a class of heterocyclic compounds that contain a pyrazole ring fused to a ketone group. Recent scientific research has focused extensively on the potential anti-inflammatory properties of pyrazolone compounds due to their diverse pharmacological effects in alleviating inflammation and reducing fever. This motivated us to focus on the preparation of these derivatives in a simple and eco-friendly manner. A convenient new green methodology was modified for the preparation of 1-phenyl-3,5-pyrazolidinedione by the sonicated MCR of diethyl malonate, phenylhydrazine, and a catalytic amount imidazole as homogenous organic catalyst in water green solvent in a good yield. On the other hand, some of 4-arylidinepyrazolidinedione derivatives are prepared in the same manner via the treatment of a mixture of diethyl malonate, phenylhydrazine, aromatic aldehydes, and a catalytic amount of imidazole in an aqueous medium. Our target synthesized pyrazolidinediones were elucidated via elemental and several spectral analyses. Due to the importance of pyrazolidinediones in the field of treating inflammation and relieving pain, a number of prepared compounds were chosen to test their efficacy as anti-inflammatory agents using carrageenan-induced foot edema in rats and compare the results with indomethacin, the standard drug. We found that the majority of derivatives yield promising results spanning from good to wonderful, so derivatives (**15k**, **15b**, **15h**, **15a**, and **15j**) yield the best results while derivative (**15i**) yields an average result. As for the derivative (**15f**), it yields the lowest results compared to the standard drug. This is due to the difference in the structural composition of these derivatives, which increases the likelihood of their use as anti-inflammatory derivatives.

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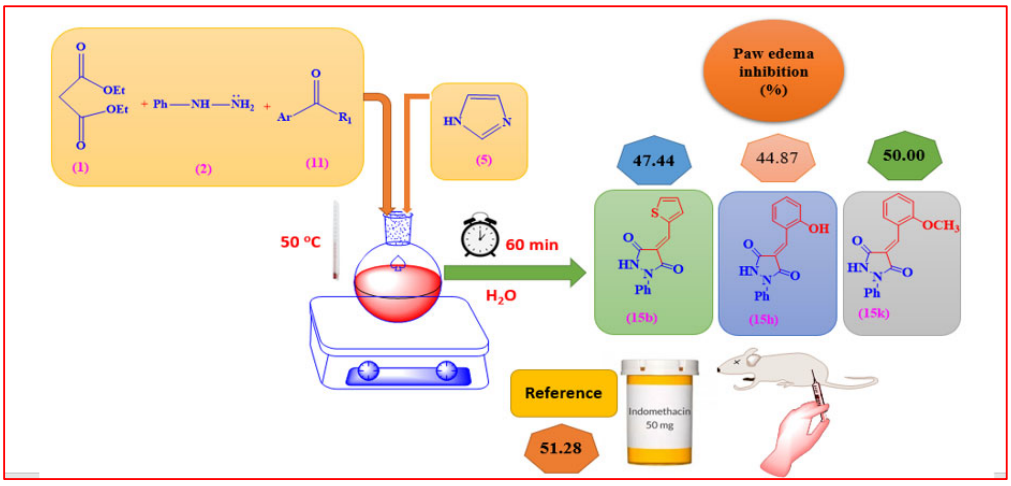


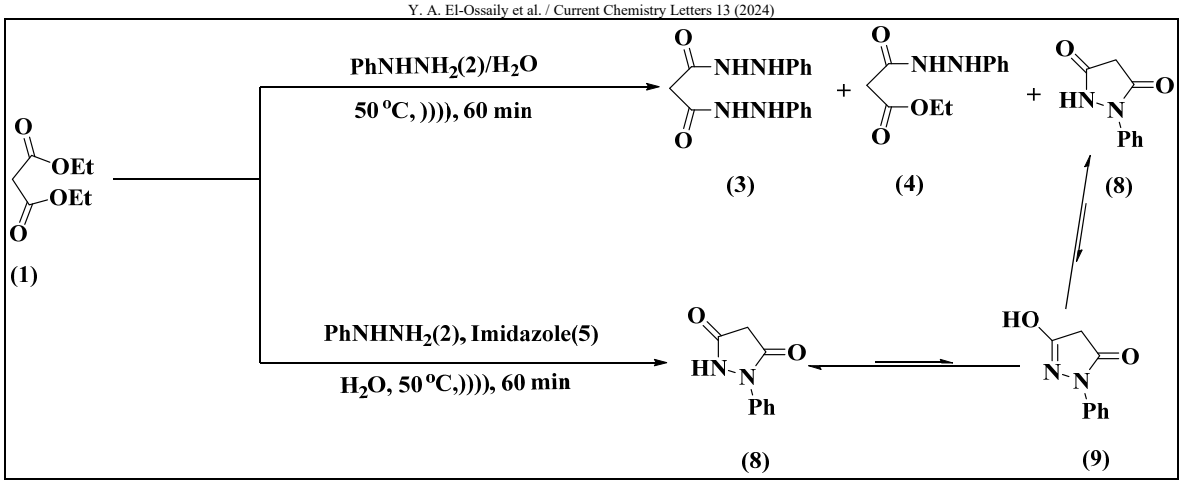
Graphical Abstract

1. Introduction

Green and sustainable chemistry, also referred to as green chemistry or sustainable chemistry, concentrates on the design, development, and application of chemical processes and products with minimal environmental impact. Throughout the life cycle of chemicals, it seeks to promote the efficient use of resources, minimize waste production, and reduce or eradicate the use of hazardous substances. Sustainable chemistry has been utilized to evaluate most chemical industries.[1] To reduce some of the environmental action of drug fabrication, there is a great interest in sustainable chemistry production.[2,3] Sustainable chemistry manufacture includes atom economy, a limited waste product, eco-friendly solvents, and chemical reagents.[4-6] And thus, the usage of water as a green solvent has increased.[7-9] The MCRs have proper features, especially atom economy, what is obey the demand for green chemistry.[10-14] Moreover, MCRs are very powerful techniques in the pharmaceutical discovery and design of profitable bioactive organic molecules. Inflammation is a complicated response to stress triggered by the body's immune system in response to a variety of detrimental stimuli, such as infections, tissue traumas, and autoimmune diseases. However, chronic or excessive inflammation can result in serious health problems. The development of effective anti-inflammatory agents has thus been the subject of extensive research.[15-20] phenylbutazone is a well-known nonsteroidal anti-inflammatory drug (NSAID) derived from pyrazolone. Scientists have been concentrating on modifying the molecular structure of pyrazolones to boost their anti-inflammatory potency while decreasing their adverse effects. The development of novel pyrazolone derivatives with enhanced anti-inflammatory activity and selectivity has involved a variety of synthetic approaches and structural modifications .Moreover, Pyrazole moiety has been considered a versatile nucleus; its analogs derivatives have been recorded to have various biological activities,[21-23] involving anti-microbial,[24] anti-fungal,[25] anti-tubercular,[26] anti-inflammatory,[27] anticonvulsant,[28] anticancer,[29] anti-viral,[30] angiotensin-converting enzymes (ACE) inhibitory, neuroprotective, cholecystokinin-1 receptor antagonist, and estrogen receptor (ER) ligand activity.[31-33] Pyrazolone derivatives have been considered the main components in anti-microbial drug discovery.[34-37] In continuation of our trials towards the improvement of green synthetic approaches for the acceleration of reaction rate in water as a green solvent and utilizing a multicomponent reactions.[38-45] Easy and practical water-assisted multicomponent reaction methodologies were described for the design of some pyrazolidindione compounds with the advantage of sustainable chemistry and the hope that have interesting biological activity applications.

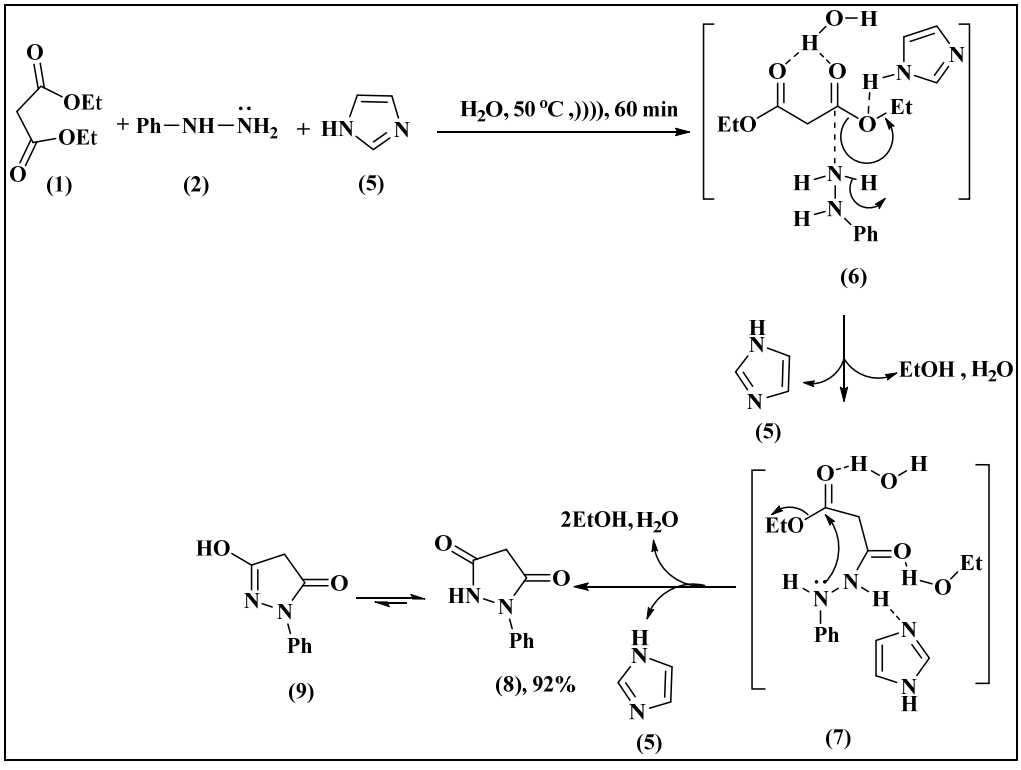
2. Result and Discussion

The proper attributes of sustainable chemistry are an efficient method, fast, simple product separation with good yields, and easy purification. These features motivated us to improve fast green methodology to synthesize Pyrazolidinedione derivative (**8**) and some of its analog derivatives hoping to have efficient biological activities. The effect of conventional polar solvents as well as the catalytic imidazole had been studieds on the reaction pathway and the percentage yield for the aim of optimizing the amount of used catalyst and assigning the performance of used solvents.At first, when the experiment had been completed without a catalyst, the pyrazolidinedione (**8**) had been obtained with low yield beside the malonic acid dihydrazide (**3**) and malonic acid monohydrazide (**4**) (Scheme1). And the addition of (0.3-1) mmol imidazole produced a poor product percentage yield of (**8**), increasing imidazole to 1.5 mmol performed (**8**) in excellent percentage yield, but increasing the amount of catalytic imidazole further did not raise the yield of the reaction. The effect of the used solvent on the production of (**8**) is firstly examined through the treatment of diethyl malonate, phenylhydrazine, and catalytic imidazole in many solvents like acetonitrile, water, methanol, ethanol, dioxane, and tetrahydrofura.[46-51] However, water provided an excellent percentage yield than their other counterparts. Compound (**8**) has been interpreted by comparing with previous reported data.[43,52,53]

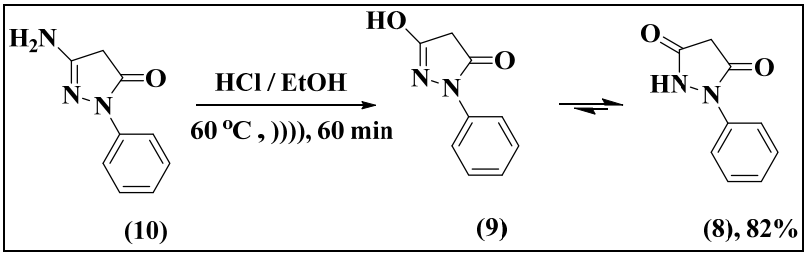


Scheme 1. Synthesis of the target 3,5-pyrazolidinedione derivative (**8**).

A reasonable reaction pathway to explain the effect of water and catalytic imidazole in the design of pyrazolidinedione derivative (**8**) had been represented in (**Scheme 2**), wherein water does electrophilic activation via hydrogen bond.[10-12,16] Structural conformation of (**8**) had been proved by comparing with previously reported data.[43] Intensive spectral analysis ascertained the dicarbonyl structure (2 hydrogenated nitrogen) (**8**) not the enol structure (**9**).

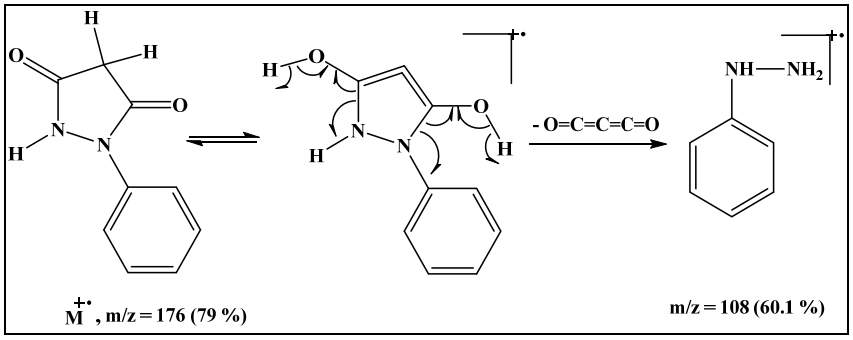


Scheme 2. The effect of water and imidazole to afford (**8**).



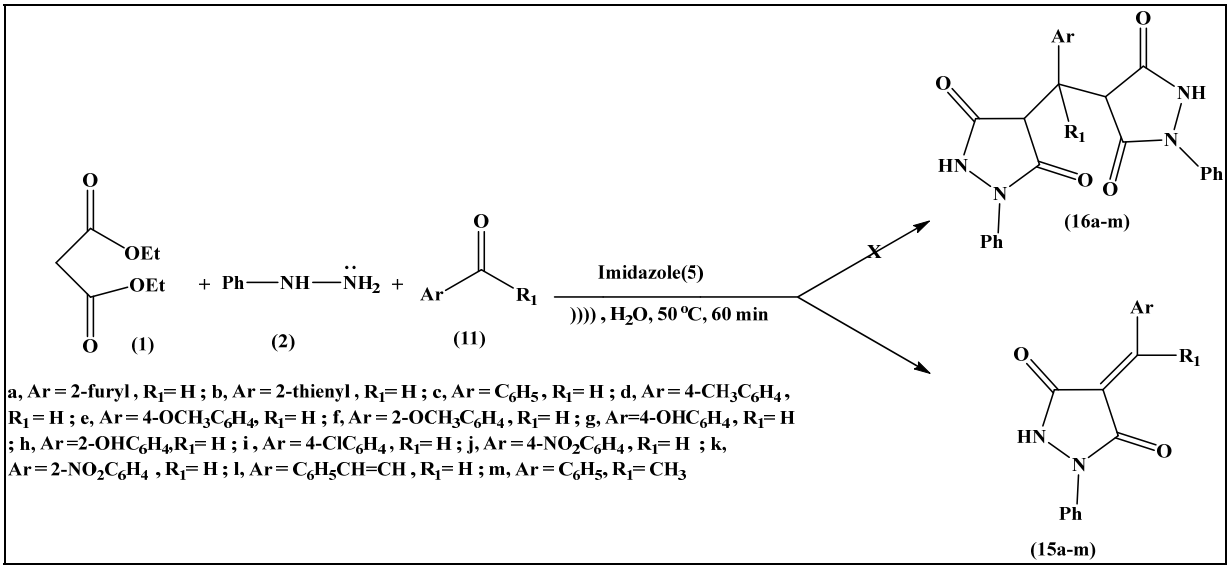
Scheme 3. Synthesis of derivative **8** from compound **10**.

Moreover, **8** was simply prepared by sonicated 1-phenyl-3-amino-2-pyrazoline-5-one (**10**) with concentrated hydrochloric acid in ethanol at 60 ° C for 1 h (Scheme 3). To get the definite structure of dicarbonlypyrazole (**8**), it was subjected to intensive spectral and chemical analysis. Elemental analysis for a highly pure sample of **8 (**as tested from TLC) proved a molecular formula of $C_9H_8N_2O_2$. Mass spectral analysis indicated an even molecular ion at 176 which is in accordance to the nitrogen rule. The relative abundance of the molecular ion (79.0%) was moderate indicating an appreciable stability of such molecular ions under electron impact (70 ev). The main fragmentation pathway represented a retro reaction leading to phenylhydrazine and carbon suboxide as required synthons for 3,5-pyrazolidinedione derivative (**8**) formation (**Scheme 4**).

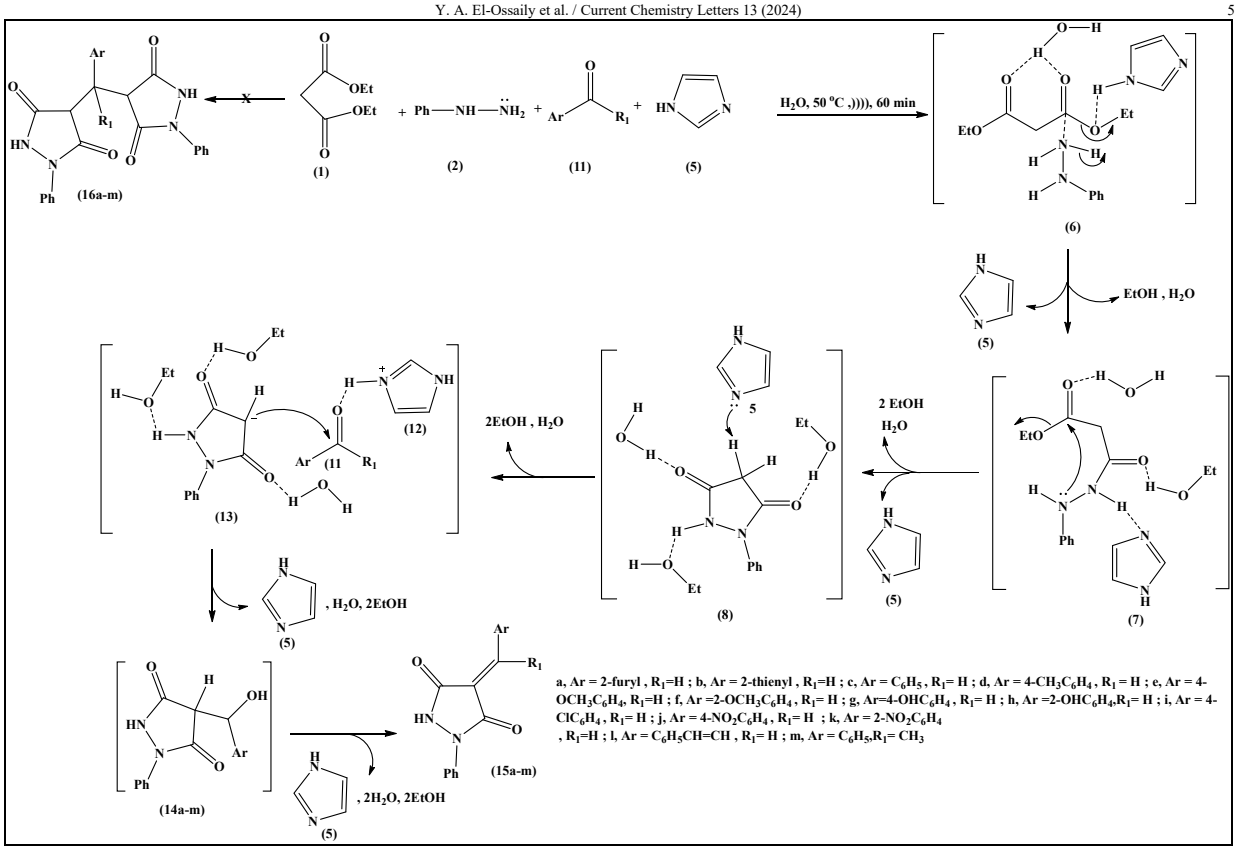


Scheme 4. The fragmentation pathway of 1-phenyl-3,5-pyrazolidinedione (**8**).

Intensive nuclear magnetic resonance as ^{1}HNMR, ^{13}CNMR, COSY, HMBC, HSQC, and DEPT-135 had proved the dicarbonyl structure (2 hydrogenated nitrogen) of **8**. DEPT-135 represented a negative (inverted) signal at δ 37.71 characteristics for ─CH_2─ group and three positive (upward) signals at 118.48, 124.83, and 124.56 characteristics for five methine carbons (═CH─). COSY, HSQC, and HMBC ascertained the neighbor protons, carbon-hydrogen connectivity, and long-range coupling (^{1}H-^{13}C correlation) via the bonds, respectively. The above spectral analyses represented an unambiguous proof for the dione structure of **8**. Our approach to the one-pot multicomponent green synthesis of our target 4-arylidinepyrazolidindione compounds was accomplished by a reaction of diethyl malonate, phenylhydrazine, various carbonyl compounds, and a catalytic amount of imidazole in presence of water as a green solvent. Here a developed methodology was performed to better the separated yield of the target compounds compared with the previous work.[54,55] Sonicated a mixture of diethyl malonate, phenylhydrazine, carbonyl compounds, and a catalytic amount of imidazole in presence of water at 50° C provided an excellent yield of pyrazolidinedione derivatives (**15a-m**) not the bis-pyrazolone derivative (**16a-m**) with excellent yield compared with previously cited literature (**Scheme 5**).[56-64] The chemical structure of 4-arylidenepyrazolidinediones (**15a-m**) was confirmed by using extensive spectral analysis as well as elemental analysis. A reasonable reaction pathway to explain the effect of water and imidazole in the synthesis of pyrazolidinedione derivatives (**15a-m**) had been shown in (**Scheme 6**) wherein water exerts electrophilic activation via hydrogen bond.

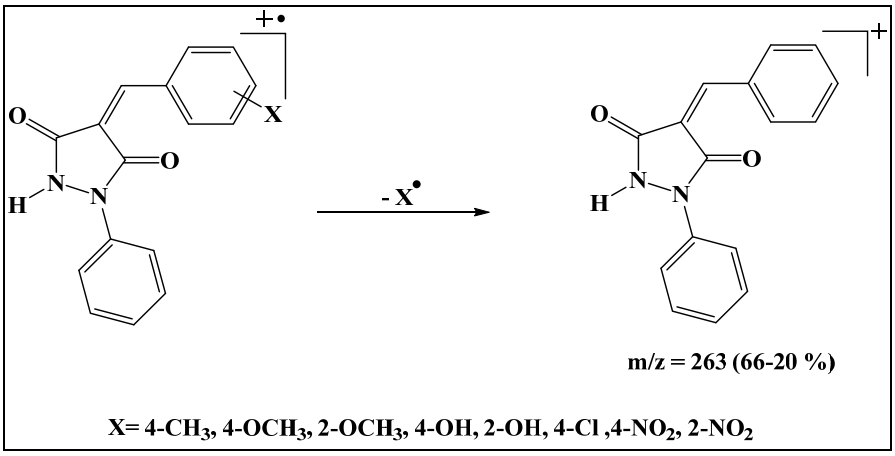


Scheme 5. The synthesis of pyrazolidinedione derivatives (**15a-m**).



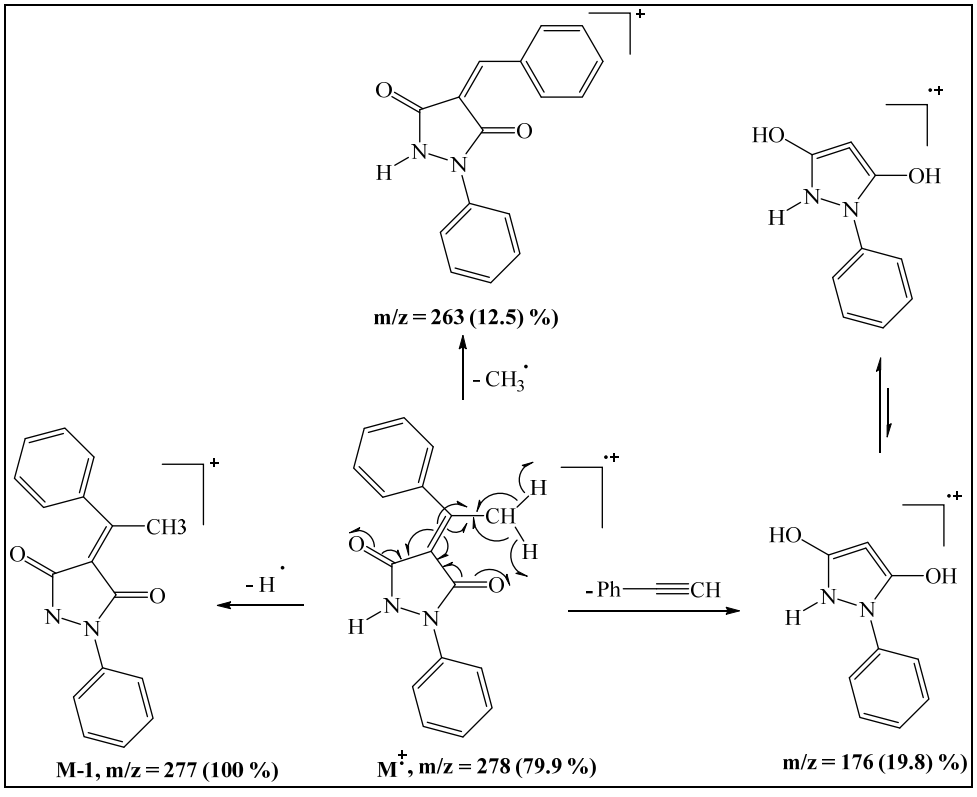
Scheme 6. The effect of water and imidazole to afford pyrazolidinedione derivatives (**15a-m**).

The 4-furfurlidene derivative (**15a**) was subjected to ^{1}H NMR measurement in DMSO-d_6 gave a multiplet at δ 6.97 ppm to 8.01 ppm including protons for SP^2 carbon atoms of phenyl and furyl groups in the molecule and a separate two singlets at δ 8.23 ppm and 8.96 ppm characteristic for =CH and NH groups respectively (**Table 2**).^{13}C NMR of 14a in DMSO-d_6 revealed the correct signals for its proposed structure as the appearance of two separate singlet signals at δ 166.43 ppm and 165.78 ppm characteristic for two carbonyl groups (**Table 2**). The mass spectrometric technique of 14a displayed a molecular ion peak at m/z 254 which represents the base peak reflecting the high stability of this molecular ion under electron impact. The FT-IR of 1-Phenyl-4-(thiophen-2-ylmethylene) pyrazolidine-3,5-dione (**15b**) exhibited the appearance of two peaks at ν 3235 and 1669 cm^{-1} characteristic for NH and 2 C=O groups, respectively. ^{1}H NMR of 15**b** in DMSO-d_6 gave a multiplet δ 6.96 ppm to δ 7.62 (8*H*, 5*H* of phenyl group and 3*H* of thienyl group) and a two singlets at δ 8.48 ppm & 10.23 ppm characteristic for =CH and NH groups respectively. In addition to ^{13}C NMR of 14b revealed two singlet signals at δ 166.01ppm and 163.89 ppm characteristics for two carbonyl groups (**Table 2**). The mass spectrometric technique of 14b displayed the molecular ion at m/z 270 which represents the base peak reflecting the high stability of this molecular ion under electron impact. Moreover, all physical, analytical, and spectral data were in convention with the suggested structures of compounds (**15c-m)** (**Tables 1** and **2**). The compound (**15f)** was subjected to extensive 2D NMR spectroscopy. The ^{1}H NMR spectra depicted a signal at δ 4.0 (3*H*, OCH_3) and a multiplet centered at δ 8.10 (11*H*, 9ArH, NH and =CH-). DEPT 135 of compound (**15f)** revealed a signal at δ 56.086 ppm characteristic for OCH_3 group and eight signals at δ 111.57 to 136.08 characteristic for SP^2 carbon atoms. As usual quaternary carbons at 120.63, 136.74 & 142.81 and 159.96 & 160.18 characteristic for carbonyl carbons. Moreover, COSY, HSQC & HMBC measurements of **15f** had shown the neighbor protons, C─H connectivity, and long-range correlation through the bonds. Most of the synthesized chalcone derivatives (**15a-m**) were subjected to mass spectrometric technique using the electron impact technique at 70 ev, most of them revealed a molecular ion peak with 100 % intensity which represents the base peak, reflecting the high stability of these molecular ions under electron impact (**Table 2**). The compounds **15d-k** showed a general fragmentation pathway through loss of the substituent group of the phenyl ring which represented the presence of a fragment ion at m/z 263 with moderate relative abundance between 66% to 20% as shown below (**Scheme 7**).



Scheme 7. The fragmentation pathway of chalcone derivatives (**15d-k**).

The mass spectrometric technique of **15m** indicated the appearance of the molecular ion at m/z 278 with fair relative intensity (79.9 %). The fragmentation pathway of **15m** under electron impact is shown in the scheme 7. The molecular ion indicated the loss of CH_3 radical to give an even ion at m/z 263 with a relative abundance of 12.5%. The main fragmentation pathway was characterized by a double Mclafferty rearrangement with loss of phenylacetylene as a neutral fragment to give the ion at m/z 176 with low relative abundance (19. 8%). The latter ion follows the same fragmentation pathway as that of compound **8** (**Scheme 8**).



Scheme 8. The fragmentation pathway of **15m**.

Table 1. Physical and elemental analysis of 4-arylidenepyrazolidinedione compounds.

Compd. no.	m.p.°C	A solvent of crystallization /Colour/Shape	Yield %	Formula / Mol. wt.	Elemental analysis
8	192 ° C	Ethanol Yellow Plates	92	$C_9H_8N_2O_2$ 176.18	Calc: C,61.36; H,4.58; N, 15.90 Found:C,61.56; H,5.21; N, 15.40
15a	235 ° C	Dioxane Dark red Flakes	85	$C_{14}H_{10}N_2O_3$ 254.25	Calc: C, 66.14; H,3.96; N, 11.02 Found:C,66.24; H,4.14; N, 10.95
15b	227 ° C	Dioxane Pale orange Granular	89	$C_{14}H_{10}N_2O_2S$ 270.31	Calc: C, 62.21; H,3.73; N, 10.36 Found:C,62.12; H,3.68; N, 10,47
15c	275 ° C	Dioxane Dark red Flakes	86	$C_{16}H_{12}N_2O_2$ 264.28	Calc:C, 72.72; H,4.58; N, 10.60 Found: C,72.58; H, 4.75; N, 10,47
15d	246° C	Dioxane Dark orange Fine Powder	87	$C_{17}H_{14}N_2O_2$ 278.31	Calc:C, 73.37; H,5.07; N, 10.07 Found:C,73.14; H,5.18; N, 10.30
15e	245 ° C	Dioxane Orange Granular	89	$C_{17}H_{14}N_2O_3$ 294.31	Calc: C,69.38; H,4.79; N, 9.52 Found:C,69.45; H,4.87; N, 9.42
15f	235 ° C	Dioxane Dark red Needles	90	$C_{17}H_{14}N_2O_3$ 294.31	Calc: C,69.38; H,4.79; N, 9.52 Found:C,69.30; H,4.86; N, 9.32
15g	280° C	Acetic acid Orange Granular	85	$C_{16}H_{12}N_2O_3$ 280.28	Calc: C, 68.56; H, 4.32; N, 9.99 Found: C,68.30; H,4.66; N, 9.77
15h	218 ° C	Acetic acid Dark red Flakes	91	$C_{16}H_{12}N_2O_3$ 280.28	Calc: C, 68.56; H, 4.32; N, 9.99 Found: C, 68.42; H,4.36; N, 10.10
15i	262 ° C	Dioxane Dark red Flakes	94	$C_{16}H_{11}ClN_2O_2$ 298.73	Calc:C, 64.33; H, 3.71; N, 9.38 Found:C, 64.42; H,3.61; N, 9.25
15j	280 ° C	Dioxane Dark brown Amorphous	95	$C_{16}H_{11}N_3O_4$ 309.28	Calc:C, 62.14; H, 3.59; N, 13.59 Found:C, 62.40; H,3.71; N, 13.59
15k	230 ° C	Dioxane Brown Granular	91	$C_{16}H_{11}N_3O_4$ 309.28	Calc: C, 62.14; H, 3.59; N, 13.59 Found:C, 62.02; H,3.84; N, 13.40
15l	245 ° C	Dioxane Dark red Flakes	87	$C_{18}H_{14}N_2O_2$ 290.32	Calc: C, 74.47; H, 4.86; N, 9.65 Found: C, 74.22; H,4.90; N, 9.80
15m	145 ° C	Dioxane Yellow Granular	82	$C_{17}H_{14}N_2O_2$ 278.31	Calc: C, 73.37; H, 5.07; N, 10.07 Found: C, 73.22; H,4.98; N, 10.23

Table 2. Spectroscopic data of 4-arylidenepyrazolidinedione compounds.

Compd. no.	IR (ν cm^{-1}) / ^{1}H-NMR δ (ppm) /^{13}CNMR δ (ppm)/ MS (m/z)
8	3250 (NH), 2900 (*SP*^{3}C-H), 1760(CO),1670(CO),1220(C-N); (DMSO-d_6): δ 3.75 (s, 2*H*, CH_2), 6.95-7.857.4 (m, 5*H*, C_6H_5) and 11.45 (s,1*H*, NH);(DMSO-d_6):δ 37.71(CH_2),118.48,124.56,128.83,136.86(C_6H_5) ,166.06 (CO) and 167.50(CO); m/z = 176 (M^+, 79%).
15a	3438(NH),1676 (CO),1597(C=C);(DMSO-d_6): δ 6.97-8.01 (m, 8*H*, C_6H_5 & furyl-*H*) , 8.23 (s, 1*H*, CH=C) and 8.96 (s,1*H*,NH); (DMSO-d_6): δ 152.18,148.77,142.16,134.55,131.49,126.56,124.98,121.84,115.51,113.09 & 104.66 (*SP*^{2} carbon atoms) ,166.43 (CO) , 165.78 (CO); m/z = 254.07 (M^+, 100%).
15b	3235(NH) and 1669(CO); (DMSO-d_6): δ 6.96 -7.62 (m, 8*H*, C_6H_5 & thienyl-*H*) , 8.48 (s,1*H*,CH=C) and 10.23 (s,1*H*, NH) ; (DMSO-d_6): δ142.54,138.62,134.43,133.28,132.09,131.55,129.47,128.14,121.33,112.65 (*SP*^{2} carbon atoms) ,166.01 (CO) , 163.89(CO) ; m/z = 270.05 (M^+, 100%).
15c	3150(NH),3050(*SP*^{2} C-H) ,1705(CO),1655(CO). (DMSO-d_6): δ 7.01-8.58 (m, 11*H*, ArH and CH=C) and 11.49 (s,1*H*, NH); (DMSO-d_6): δ 149.62,136.54,134.05,133.40,132.29,129.92,124.79,119.88,118.34 (*SP*^{2} carbon atoms) ,160.34 (CO), 162.96(CO) ; m/z = 264 (M^+, 100%).
15d	3200(NH),30٢0(*SP*^{2} C-H), ٢٨٥0 (*SP*^{3} C-H), 1700 (CO),1655(CO);(DMSO-d_6): δ 2.4(s,3*H*, CH_3), δ 6.60-8.30 (m, 10*H*, 9ArH and CH=C) and 11.40 (s,1*H*, NH); (DMSO-d_6): δ 21.52(CH_3), 118.34,124.76,128.87,129.88,129.54134.47136.66,144.62, 150.07,158.87(*SP*^{2} carbon atoms) ,160.66 (CO) and 163.88(CO) ; m/z = 278 (M^+, 100%).
15e	3150(NH),30٢0(*SP*^{2} C-H), ٢٨٥0 (*SP*^{3} C-H), 1700 (CO),1650(CO) ; (DMSO-d_6): δ 3.9 (s,3*H*, OCH_3), multiplet centered at 7.88 (m, 10*H*, 9ArH and CH=C) and 11.24(s,1*H*, NH); (DMSO-d_6): δ 55.71(OCH_3), 114.4,116.06,118.24,118.76,124.56,125.49,137.25,128.88,149.91,159.26 (*SP*^{2} carbon atoms) ,161.05(CO),163.89 (CO) ; m/z = 294 (M^+, 100%).
15f	3200(NH),3040(*SP*^{2} C-H), ٢٨٥0 (*SP*^{3} C-H), 1700 (CO),1655(CO);(DMSO-d_6): δ 4.0(s,3*H*, OCH_3), multiplet centered at 8.10 (m, 10*H*, 9ArH and CH=C) and 11.45 (s,1*H*, NH); (DMSO-d_6): δ 56.08(OCH_3), 111.57,118.76,120.24,120.63,124.63128.89,133.51,136.08,136.64,142.81,158.79 (*SP*^{2} carbon atoms) ,159.96(CO),160.71 (CO) ; m/z = 294 (M^+, 100%).
15g	3220(OH),3150(NH),3010(*SP*^{2} C-H), 1690 (CO),1650(CO);(DMSO-d_6): δ 6.80-8.70 (m, 12*H*, 9ArH, CH=C, NH and OH) ; m/z = 280 (M^+, 100%).
15h	3310(OH),3150(NH),3050(*SP*^{2} C-H), 1695 (CO),1650(CO);(DMSO-d_6): δ 9.20(s,1*H*, OH), 6.80-9.2 (m, 10*H*, 9ArH and CH=C) and 10.95 (s,1*H*, NH) ; (DMSO-d_6): δ 116.04,117.26,118.76,119.50,124.59,128.91,133.47,136.79,137.15,143.70,159.88, (*SP*^{2} carbon atoms) ,159.16(CO),160.09 (CO) ; m/z = 280(M^+, 100%).
15i	3150(NH),3040(*SP*^{2} C-H),1710 (CO),1660(CO);(DMSO-d_6): multiplet centered at δ 7.95 (m, 10*H*, 9ArH and CH=C) and 11.55 (s,1*H*, NH); (DMSO-d_6): δ118.38,120.23,124.87,129.25,131.17,135.63,135.72,136.47,138.15(*SP*^{2} carbon atoms) ,158.48(CO),160.13 (CO) ; m/z = 298(M^+, Cl 35, 100%), 300(M^+, Cl 37, 37.20%).
15j	3150(NH),3040(*SP*^{2} C-H), 1700 (CO),1660(CO); (DMSO-d_6): multiplet centered at δ 7.90 (m, 10*H*, 9ArH and CH=C) and 10.20 (s,1*H*, NH); (DMSO-d_6): δ118.88,123.42,125.01129.00,130.62,134.51,136.54,137.93, 147.62 (*SP*^{2} carbon atoms) ,159.59(CO),161.04 (CO) ; m/z = 309 (M^+, 100%).
15k	3100(NH),3010(*SP*^{2} C-H), 1710 (CO),1670(CO); (DMSO-d_6): δ 11.6 (s, 1*H*, NH), multiplet centered at 7.75 (m, 10*H*, 9ArH and CH=C);(DMSO-d_6): δ 118.56,124.85,127.95,128.87,129.82,132,62,136.72,145.31,147.69,157.84 (*SP*^{2} carbon atoms) ,159.41(CO),160.57 (CO) ; m/z = 309(M^+, 42.6%).
15l	3400(NH),3040(*SP*^{2} C-H), 1700 (CO),1650(CO); (DMSO-d_6): δ7.20-8.40 (m, 14*H*, 10ArH, 3 =CH and NH); (DMSO-d_6): δ118.23,122.10,122.48,124.50,128.42,129.28,131.10, 135.18,137.00,151.01(*SP*^{2} carbon atoms) ,160.16(CO),162.06 (CO).
15m	3150(NH),3040(*SP*^{2} C-H), 2900(*SP*^{3} C-H), 1740 (CO),1650(CO); (DMSO-d_6): δ 2.75(s,3*H*,CH_3), multiplet centered at 7.50 (m, 10*H* and 9ArH) and 11.55 (s,1*H*, NH); DMSO-d_6): δ 27.69(CH_3),118.42,119.25,124.53,127.65,128.81,128.42,128.42,129.28,131.10,136.82 135.18,137.00,151.01(*SP*^{2} carbon atoms) ,166.06(CO),167.47 (CO) ; m/z = 278(M^+, 70.90%).

2.1 Biological Activity

2.1.1 Anti-inflammatory Activity

Statistical analysis

The outcomes had been evaluated using one-way ANOVA, accompanied by the Newman–Keuls multiple comparison experiments as a post-test. The calculations were done employing the Prism computer program for Windows 3.0. (GraphPad Software, Inc, San Diago CA, USA). P\0.05*, 0.01**, or 0.001*** was accepted as a significant difference between the groups. **Table 3** shows the reduction in the width of rat paw edema (mm) resulting from the impact of the tested derivatives over time when compared to the reference compound (indomethacin). **Figure 1** depicts a plot depicting the reduction in the width of paw edema inhibition in rats resulting from the action of indomethacin and the examined compounds over time. The inflammatory response has been shown by the time course of the percentage increase in foot swelling, the area under the curve response, and the percentages of foot edema suppression.

The accompanying ratio was used to estimate each chemical at each time point: Percentage of edema inhibition Percent edema inhibition = (Vc −Vt / Vc) ∗100

Vc: is the volume of paw edema in negative control immediately after carrageenan injection, Vt: is the volume of paw edema in the treated group. **Table 2** and **Figure 2** show an improvement in the percentage of paw edema inhibition for the investigated derivatives when compared to the standard (indomethacin).

The effectiveness of the examined derivatives was determined using the following equation in comparison to the indomethacin:

Potency = Percentage edema inhibition of tested compound treated group / Percentage edema inhibition of indomethacin treated group

Based on earlier findings, we discovered that several of the evaluated substances had substantial anti-inflammatory efficacy when compared to indomethacin. For example, during the control period, the size of the edema is the same, and after 30 minutes, there is no considerable variation in the size of the edema between indomethacin and the examined substances. As displayed in **Tables 4** and **5** and **Fig. 2**, after 1 hour all derivatives exhibited considerable variations from indomethacin, with compounds **15j** and **15k** showing the least significant difference from the other tested substance, implying that compounds **15f** and **15i** had similar effects to indomethacin. **15b** exhibited no significance from indomethacin after 3 h., but the chalcone derivatives **15a** and **15j** represented low importance (P\0.05). Compounds **15f**, **15b, 15h**, **15j**, and **15k** exhibited a low meaningful variation from the reference substance after 4 hours (P\0.05). In general, compounds **15a**, **15b, 15h**, **15j**, and **15k** were the most successful, active, and quick derivatives for the treatment of inflammation, whereas compound **15i** yielded outcomes ranging from good to medium after 4 hours. Finally, whereas derivative **15f** had poor efficacy in treating this form of inflammation, its anti-inflammatory action was equivalent to that of indomethacin.

Table 3. The impact of chalcone derivatives (**15a, 15b, 15f, 15h, 15i, 15j,** and **15k**) on carrageenan-induced paw edema in rats (zone of inhibition in mm)

Compounds The thickness of rat paw edema (mm)									
Time (h)	Negative control	Indomethacin	**15a**	**15b**	**15f**	**15h**	**15i**	**15j**	**15k**
		←	(0.028 mmol)			(0.025 mmol)	→		
0.5	0.75±0.00	0.63±0.06	0.70±0.00	0.73±0.03	0.73±0.03	0.72±0.03	0.71±0.03	0.71±0.03	0.71±0.03
1	0.76±0.03	0.49±0.05	0.60±0.04	0.66±0.03	0.70±0.00	0.65±0.04	0.65±0.05	0.56±0.06	0.61±0.05
2	0.77±0.03	0.40±0.04	0.51±0.07	0.51±0.06	0.70±0.04	0.54±0.09	0.53±0.05	0.49±0.06	0.43±0.05
3	0.78±0.06	0.39±0.05	0.50±0.04	0.48±0.03	0.70±0.04	0.44±0.05	0.49±0.03	0.44±0.05	0.41±0.03
4	0.78±0.03	0.38±0.03	0.46±0.05	0.41±0.03	0.70±0.04	0.43±0.05	0.49±0.05	0.46±0.03	0.39±0.03

Table 4. The increase in percentage of edema inhibition (%) of compounds (**15a, 15b, 15f, 15h, 15i, 15j,** and **15k**) with time (h).

	Paw edema inhibition (%)							
Time (h)	Indomethacin	**15a**	**15b**	**15f**	**15h**	**15i**	**15j**	**15k**
0.5	16.00	6.67	2	2	4.00	5.33	5.33	5.33
1	35.52	16.00	13.15	7.89	14.47	14.47	20.00	19.73
2	48.05	33.77	33.77	9.09	29.87	31.17	36.36	44.16
3	50.00	35.90	38.46	10.26	43.59	37.18	43.59	47.44
4	51.28	41.03	47.44	10.26	44.87	37.18	41.03	50.00

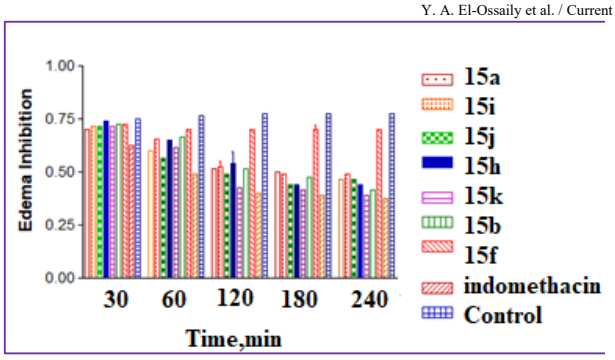


Fig. 1. A plot of edema inhibition (mm) of compounds (**15a, 15b, 15f, 15h, 15i, 15j,** and **15k**) with time.

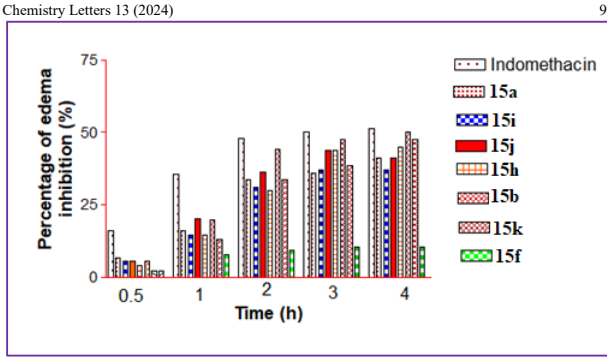


Fig. 2. A diagram represents the increase in the percentage of edema inhibition (%) compounds (**15a, 15b, 15f, 15h, 15i, 15j,** and **15k**) with time (h)

Table 5. The potency of compounds (**15a, 15b, 15f, 15h, 15i, 15j,** and **15k**) relative to indomethacin.

Time (h)	Potency relative to indomethacin						
	15a	**15b**	**15f**	**15h**	**15i**	**15j**	**15k**
0.5	0.42	0.13	0.13	0.25	0.33	0.33	0.33
1	0.45	0.37	0.22	0.41	0.41	0.56	0.56
2	0.70	0.70	0.19	0.62	0.65	0.76	0.92
3	0.72	0.77	0.20	0.87	0.74	0.87	0.95
4	0.80	0.93	0.20	0.88	0.73	0.80	0.98

3. Experimental

Melting points were determined on a GmbH-VarioEL V.3 micro-analyzer electro-thermal melting point apparatus and are uncorrected. FT-IR spectra were recorded as potassium bromide disks using Pye-Unicam Sp-100 infrared spectrophotometer.^{1}H-NMR and ^{13}C-NMR spectra were carried on Jeol 400 MHz spectrometer andin DMSO-d6 using Me_4Si as internal standard, and chemical shifts were expressed as ppm. JEOL JMS-600 and Hewlett-Packard model MS 5988 Spectrometers were used for the determination of mass spectra.CHN microanalyses were conducted using a Perkin Elmer 2400 LS Series CHN/O Analyser. TLC was carried out on aluminium-backed silica gel plates (Merck $60F_{254}$) and visualized under short-wave UV light. Reactions performed at air atmosphere.

Synthesis of 1-Phenyl-3,5-pyrazolidinedione (8)

a) From diethylmalonate, phenylhydrazine and Imidazole

A mixture of 10 mmol of diethylmalonate, 10 mmol of phenylhydrazine, and 1.5 mmol of imidazole in water (30 ml) were sonicated at 50 ºC for one hour. After cooling, the formed precipitate was filtered and purified by crystallization from ethanol as pale-yellow plate crystals. m.p.193-195 ºC (Lit. 192 ºC), yield (92%).[40]

b) From 1-phenyl-3-amino-5-pyrazolone.

A suspension of 1-phenyl-3-amino-5-pyrazolone (29.8 mmol) in a mixture of 25 ml of water, 15 ml of ethanol, and 3.6 ml of concentrated hydrochloric acid was sonicated for one hour at 60 ºC. After cooling, the resulting product was filtered, collected, and recrystallized from ethanol as pale-yellow plates, yielding (82%).

Synthesis of (E/Z) 4- arylidenepyrazolidinediones (15a-m) (general method):

Sonication of a mixture of diethylmalonate (10 mmol), phenylhydrazine (10 mmol), carbonyl compounds (10 mmol), and a catalytic amount of imidazole (1.5 mmol) in presence of 30 ml of water for one hour at 50 ºC. After cooling, the formed product was filtered, collected, and recrystallized from the proper solvent. Compounds (**15a-m**) were separated in good yields (82 - 95 %) (**Tables 1** and **2**). This work confirms that there are different applications for heterocyclic compounds which is reflected in many papers that have been published before.[65-107]

4. Conclusion

Encouraged by the exhaustive review of the literature, the outstanding anti-inflammatory properties of pyrazolone compounds were discovered. Additionally, the researchers focused on modifying the chemical structure of pyrazolones to improve their anti-inflammatory efficacy and selectivity while minimizing adverse effects. Therefore, we prepared these compounds in a simple manner by combining an eco-friendly solvent with an imidazole catalyst. And we demonstrated the chemical structures of the derivatives produced by a variety of methodologies, as well as their mechanisms of action, structure, and activity relationships. We discovered that the majority of the derivatives depicted in **Tables 3** and **4** exhibit

remarkable results. For instance, the derivatives (**15k**, **15b**, **15h**, **15a**, and **15j**) are the most effective at alleviating inflammation paw edema caused by carrageenan in rats, whereas the derivative (**15i**) produced an acceptable result. While the derivative (**15f**) demonstrated the poorest performance in comparison to the standard drug, indomethacin. This is due to the structural differences between these derivatives, which increase their potential as anti-inflammatory agents.

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References

(1) Tundo P., Anastas P., Black D. S., Breen J., Collins T. J., Memoli S., Miyamoto J., Polyakoff M., and Tumas, W. (**2000**) Synthetic pathways and processes in green chemistry. Introductory overview. *Pure Appl. Chem.*, 72 (7) 1207-1228.

(2) Alfonsi K., Colberg J., Dunn P. J., Fevig T., Jennings S., Johnson T. A., ... and Stefaniak M. (**2008**) Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation. *Green Chem.*, 10 (1) 31-36.

(3) Roughley S. D., and Jordan A. M. (**2011**) The medicinal chemist's toolbox: an analysis of reactions used in the pursuit of drug candidates. *J. Med. Chem.*, 54 (10) 3451-3479.

(4) Parikh N., Roy S. R., Seth K., Kumar A., and Chakraborti A. K. (**2016**) 'On-water'multicomponent reaction for the diastereoselective synthesis of functionalized tetrahydropyridines and mechanistic insight. *Synthesis*, 48 (04) 547-556.

(5) Jadhavar P. S., Dhameliya T. M., Vaja M. D., Kumar D., Sridevi J. P., Yogeeswari P., ... and Chakraborti A. K. (**2016**) Synthesis, biological evaluation and structure–activity relationship of 2-styrylquinazolones as anti-tubercular agents. *Bioorg. Med. Chem. Lett.*, 26 (11) 2663-2669.

(6) Kumar D., Jadhavar P. S., Nautiyal M., Sharma H., Meena P. K., Adane L., ... and Chakraborti A. K. (**2015**) Convenient synthesis of 2, 3-disubstituted quinazolin-4 (3 H)-ones and 2-styryl-3-substituted quinazolin-4 (3 H)-ones: Applications towards the synthesis of drugs. *RSC Adv.*, 5 (39) 30819-30825.

(7) Kumar D., Kumar A., Qadri M. M., Ansari M. I., Gautam A., and Chakraborti A. K. (**2015**) In (OTf) 3-catalyzed synthesis of 2-styryl quinolines: scope and limitations of metal Lewis acids for tandem Friedländer annulation–Knoevenagel condensation. *RSC Adv.*, 5 (4) 2920-2927.

(8) Kumar D., Sonawane M., Pujala B., Jain V. K., Bhagat S., and Chakraborti A. K. (**2013**) Supported protic acid-catalyzed synthesis of 2, 3-disubstituted thiazolidin-4-ones: enhancement of the catalytic potential of protic acid by adsorption on solid supports. *Green Chem.*, 15 (10) 2872-2884.

(9) Kumar D., Kommi D. N., Bollineni N., Patel A. R., and Chakraborti A. K. (**2012**) Catalytic procedures for multicomponent synthesis of imidazoles: selectivity control during the competitive formation of tri-and tetrasubstituted imidazoles. *Green Chem.*, 14 (7) 2038-2049.

(10) Khatik G. L., Kumar R., and Chakraborti A. K. (**2006**) Catalyst-free conjugated addition of thiols to α, β-unsaturated carbonyl compounds in water. *Org. Lett.*, 8 (11) 2433-2436.

(11) Chankeshwara S. V., and Chakraborti A. K. (**2006**) Catalyst-free chemoselective N-tert-butyloxycarbonylation of amines in water. *Org. Lett.*, 8 (15) 3259-3262.

(12) Chakraborti A. K., Rudrawar S., Jadhav K. B., Kaur G., and Chankeshwara S. V. (**2007**) "On water" organic synthesis: a highly efficient and clean synthesis of 2-aryl/heteroaryl/styryl benzothiazoles and 2-alkyl/aryl alkyl benzothiazolines. *Green Chem.*, 9 (12) 1335-1340.

(13) Sharma G., Kumar R., and Chakraborti A. K. (**2008**) 'On water'synthesis of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines catalysed by sodium dodecyl sulfate (SDS). *Tetrahedron Lett.*, 49 (27) 4269-4271.

(14) RahaáRoy S. (**2011**) Surfactant mediated oxygen reuptake in water for green aerobic oxidation: mass-spectrometric determination of discrete intermediates to correlate oxygen uptake with oxidation efficiency. *Chem. Commun.*, 47 (6) 1797-1799.

(15) Kommi D. N., Kumar D., Bansal R., Chebolu R., and Chakraborti A. K. (**2012**) "All-water" chemistry of tandem N-alkylation–reduction–condensation for synthesis of *N*-arylmethyl-2-substituted benzimidazoles. *Green Chem.*, 14 (12) 3329-3335.

(16) Kommi D. N., Jadhavar P. S., Kumar D., and Chakraborti A. K. (**2013**) "All-water" one-pot diverse synthesis of 1, 2-disubstituted benzimidazoles: hydrogen bond driven 'synergistic electrophile–nucleophile dual activation'by water. *Green Chem.*, 15 (3) 798-810.

(17) Kommi D. N., Kumar D., and Chakraborti A. K. (**2013**) "All water chemistry" for a concise total synthesis of the novel class anti-anginal drug (RS),(R), and (S)-ranolazine. *Green Chem.*, 15 (3) 756-767.

(18) Kumar D., Seth K., Kommi D. N., Bhagat S., and Chakraborti A. K. (**2013**) Surfactant micelles as microreactors for the synthesis of quinoxalines in water: scope and limitations of surfactant catalysis. *RSC Adv.*, 3 (35) 15157-15168.

(19) Tanwar B., Purohit P., Raju B. N., Kumar D., Kommi D. N., and Chakraborti A. K. (**2015**) An "all-water" strategy for regiocontrolled synthesis of 2-aryl quinoxalines. *RSC Adv.*, 5 (16) 11873-11883.

(20) Dhameliya T. M., Chourasiya S. S., Mishra E., Jadhavar P. S., Bharatam P. V., and Chakraborti A. K. (**2017**) Rationalization of benzazole-2-carboxylate versus benzazine-3-one/benzazine-2, 3-dione selectivity switch during cyclocondensation of 2-aminothiophenols/phenols/anilines with 1, 2-biselectrophiles in aqueous medium. *J. Org. Chem.*, 82 (19) 10077-10091.

(21) Lee C. S., Allwine D. A., Barbachyn M. R., Grega K. C., Dolak L. A., Ford C. W., ... and Genin M. J. (**2001**) Carbon–carbon-linked (pyrazolylphenyl) oxazolidinones with antibacterial activity against multiple drug resistant gram-positive and fastidious gram-negative bacteria. *Bioorg. Med. Chem.*, 9 (12) 3243-3253.
(22) Sridhar R., Perumal P. T., Etti S., Shanmugam G., Ponnuswamy M. N., Prabavathy V. R., and Mathivanan N. (**2004**) Design, synthesis and anti-microbial activity of 1H-pyrazole carboxylates. *Bioorg. Med. Chem. Lett.*, 14 (24) 6035-6040.
(23) Ismail Z. H., Abdel-Gawad S. M., Abdel-Aziem A., and Ghorab M. M. (**2003**) Synthesis of some new biologically active sulfur compounds containing pyrazolo [3,4-*d*] pyrimidine moiety. *Phosphorus. Sulfur. Silicon Relat. Elem.*, 178 (8) 1795-1805.
(24) Mamolo M. G., Falagiani V., Zampieri D., Vio L., and Banfi E. (**2001**) Synthesis and antimycobacterial activity of [5-(pyridin-2-yl)-1, 3, 4-thiadiazol-2-ylthio] acetic acid arylidene-hydrazide derivatives. *Farm.*, 56 (8) 587-592.
(25) Hassan S. Y. (**2013**) Synthesis, antibacterial and antifungal activity of some new pyrazoline and pyrazole derivatives. *Molecules*, 18 (3) 2683-2711.
(26) Barnes B. J., Eakin A. E., Izydore R. A., and Hall I. H. (**2000**) Selective Inhibition of Human Molt-4 Leukemia Type II Inosine 5 '-Monophosphate Dehydrogenase by the 1,5-Diazabicyclo [3.1.0] hexane-2,4-diones. *Biochemistry*, 39 (45) 13641-13650.
(27) Dilek Altıntop M., Ozdemir A., Ilgın S., and Atli O. (**2014**) Synthesis and biological evaluation of new pyrazole-based thiazolyl hydrazone derivatives as potential anticancer agents. *Lett. Drug Des. Discov.*, 11 (7) 833-839.
(28) Baraldi P. G., Pavani M. G., del Carmen Nunez M., Brigidi P., Vitali B., Gambari R., and Romagnoli R. (**2002**) Antimicrobial and antitumor activity of N-heteroimmine-1, 2, 3-dithiazoles and their transformation in triazolo-, imidazo-, and pyrazolopirimidines. *Bioorg. Med. Chem.*, 10 (2) 449-456.
(29) Ochi T., Yamane-Sugiyama A., Ohkubo Y., Sakane K., and Tanaka H. (**2001**) The anti-inflammatory effect of FR188582, a highly selective inhibitor of cyclooxygenase-2, with an ulcerogenic sparing effect in rats. *Jpn. J. Pharmacol.*, 85 (2) 175-182.
(30) Abdel-Aziz M., Abuo-Rahma G. E. D. A., and Hassan A. A. (**2009**) Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activities. *Eur. J. Med. Chem.*, 44 (9) 3480-3487.
(31) Pyo S. G. (**2014**) Characterization and Formation of Selectively Deposited Solar Electrode Using Electroless Plating Process. In *Electrochemical Society Meeting Abstracts ecee2014* (No. 3, pp. 427-427). The Electrochemical Society, Inc.
(32) Baraldi P. G., Bovero A., Fruttarolo F., Romagnoli R., Tabrizi M. A., Preti D., ... and Moorman A. R. (**2003**) New strategies for the synthesis of A3 adenosine receptor antagonists. *Bioorg. Med. Chem.*, 11 (19) 4161-4169.
(33) El-Sabbagh O. I., Baraka M. M., Ibrahim S. M., Pannecouque C., Andrei G., Snoeck R., ... and Rashad A. A. (**2009**) Synthesis and antiviral activity of new pyrazole and thiazole derivatives. *Eur. J. Med. Chem.*, 44 (9) 3746-3753.
(34) Sayed M., Kamal El-Dean A. M., Ahmed M., and Hassanien R. (**2018**) Synthesis, Characterization, and Screening for Anti-inflammatory and Antimicrobial Activity of Novel Indolyl Chalcone Derivatives. *J. Heterocycl. Chem.*, 55 (5) 1166-1175.
(35) Tolba M. S., Abdul-Malik M. A., Kamal El-Dean A. M., Geies A. A., Radwan Sh. M., Zaki R. M., Sayed M., Mohamed S. K., and Abdel-Raheem Sh. A. A. (**2022**) An overview on synthesis and reactions of coumarin based compounds. *Curr. Chem. Lett.*, 11 (1) 29-42.
(36) Tolba M. S., Kamal El-Dean A. M., Ahmed M., Hassanien R., Sayed M., Zaki R. M., Mohamed S. K., Zawam S. A., and Abdel-Raheem Sh. A. A. (**2022**) Synthesis, reactions, and applications of pyrimidine derivatives. *Curr. Chem. Lett.*, 11 (1) 121-138.
(37) Tolba M. S., Sayed M., Abdel-Raheem Sh. A. A., Gaber T. A., Kamal El-Dean A. M., and Ahmed M. (**2021**) Synthesis and spectral characterization of some new thiazolopyrimidine derivatives. *Curr. Chem. Lett.*, 10 (4) 471-478.
(38) El-Zohry M. F., Younes M. I., and Metwally S. A. (**1984**) Synthesis and some reactions of 3-methyl-2-pyrazolin-4, 5-dione. *Synthesis (Stuttg)*, 11 972-974.
(39) Metwally S. A., Mahfouz R. M., Elossaily Y. A., Aref S. A., and Naffea Y. A. (**2016**) Interaction of tetracyanoethylene (TCE) with active methylene compounds: synthesis, reactions and spectral characterization of some novel 2-pyrazoline-5-one compounds. Computational studies on the synthesized molecules by DFT. *Assiut Univ. J. Chem.*, 45 33-46.
(40) El-Ossaily Y. A., Metwally S. A., Al-Muailkel N. S., Fawzy A., Ali H. M., and Naffea Y. A. (**2020**) Green synthetic investigation and spectral characterization of some spiro pyrazolidine-based heterocycles with potential biological activity. *J. Heterocycl. Chem.*, 57 (4) 1729-1736.
(41) Drück U., and Littke W. (**1980**) The structures of two rubazoic acid derivatives. *Acta Crystallogr. Sect. B Struct. Crystallogr. Cryst. Chem.*, 36 (12) 3002-3007.
(42) Kirschke K., Hübner P., Lutze G., Gründemann E., and Ramm M. (**1994**) Ringtransformationen von 1-Oxa-5, 6-diazaspiro [2.4] hept-6-en-4-onen zu 4,5-Dihydro-4-hydroxy-1H-pyrazol-4-carbonsäure-Derivaten. *Liebigs Ann. Der Chemie.*, 1994 (2) 159-165.
(43) Metwally S. A. M., Mohamed T. A., Moustafa O. S., and El-Ossaily Y. A. (**2011**) Novel synthesis of highly functionalized pyrazolone systems via rearrangement of 5-phenyl-1-oxa-5,6-diazaspiro [2.4] heptane-4,7-diones. *Chem. Heterocycl. Compd.*, 46 1344-1353.
(44) Younis O., Al-Hossainy A. F., Sayed M., El-dean A. M. K., and Tolba M. S. (**2022**) Synthesis and intriguing single-component white-light emission from oxadiazole or thiadiazole integrated with coumarin luminescent core. *J. Photochem. Photobiol. A Chem.*, 431 113992.

(45) Mohamed S. K., El Bakri Y., Abdul D. A., Ahmad S., Albayati M. R., Lai C. H., ... and Tolba M. S. (**2022**) Synthesis, crystal structure, and a molecular modeling approach to identify effective antiviral hydrazide derivative against the main protease of SARS-CoV-2. *J. Mol. Struct.*, 1265 133391.

(46) Siddekha A., Nizam A., and Pasha M. A. (**2011**) An efficient and simple approach for the synthesis of pyranopyrazoles using imidazole (catalytic) in aqueous medium, and the vibrational spectroscopic studies on 6-amino-4-(4′-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c] pyrazole using density functional theory. *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.*, 81 (1) 431-440.

(47) Kalla R. M. N., and Kim I. (**2019**) Highly efficient synthesis of pyrazolylphosphonate derivatives in biocompatible deep eutectic solvent. *Mol. Catal.*, 473 110396.

(48) Martina K., Tagliapietra S., Veselov V. V., and Cravotto G. (**2019**) Green protocols in heterocycle syntheses via 1, 3-dipolar cycloadditions. *Front. Chem.*, 7 95.

(49) Dekhici M., Plihon S., Bar N., Villemin D., Elsiblani H., and Cheikh N. (**2019**) Aerobic Copper Catalytic Oxidation of Methylene and Arylidenebisnaphthols: A Green and Efficient Synthesis of Spironaphthalenones. *ChemistrySelect*, 4 (2) 705-708.

(50) Shultz M. J., and Vu T. H. (**2015**) Hydrogen bonding between water and tetrahydrofuran relevant to clathrate formation. *J. Phys. Chem. B.*, 119 (29) 9167-9172.

(51) Carvalho J. F., Silva M. M. C., and e Melo M. L. S. (**2009**) Highly efficient epoxidation of unsaturated steroids using magnesium bis (monoperoxyphthalate) hexahydrate. *Tetrahedron*, 65 (14) 2773-2781.

(52) Hamed M. M., Sayed M., Abdel-Mohsen S. A., Saddik A. A., Ibrahim O. A., El-Dean A. M. K., and Tolba M. S. (**2023**) Synthesis, biological evaluation, and molecular docking studies of novel diclofenac derivatives as antibacterial agents. *J. Mol. Struct.*, 1273 134371.

(53) Almutlaq N., Elshanawany M. M., Sayed M., Younis O., Ahmed M., Wachtveitl J., ... and Abozeed A. A. (**2023**) Synthesis, structural, TD-DFT, and optical characteristics of indole derivatives. *Curr. Appl. Phys.*, 45 86-98.

(54) Hussein E. M., Ahmed S. A., Guesmi N. E., and Khairou K. S. (**2017**) 1,3-Dipolar cycloaddition approach to novel dispiro [pyrazolidine-4,3′-pyrrolizidine-2′,3″-indoline]-2″,3,5-triones. *J. Chem. Res.*, 41 (6) 346-351.

(55) Kamal R., Kumar R., Kumar V., and Bhardwaj V. (**2019**) Synthetic Utilization of α, β-Chalcone Dibromide In Heterocyclic Chemistry and Stereoselective Debromination. *ChemistrySelect*, 4 (39) 11578-11603.

(56) Hsieh C. Y., Ko P. W., Chang Y. J., Kapoor M., Liang Y. C., Chu H. L., ... and Hsu M. H. (**2019**) Design and synthesis of benzimidazole-chalcone derivatives as potential anticancer agents. *Molecules*, 24 (18) 3259.

(57) Zimmerman H. E., Singer L., and Thyagarajan B. S. (**1959**) Overlap control of carbanionoid reactions. I. stereoselectivity in alkaline epoxidation. *J. Am. Chem. Soc.*, 81 (1) 108-116.

(58) Singleton D. A., Merrigan S. R., Liu J., and Houk K. N. (**1997**) Experimental geometry of the epoxidation transition state. *J. Am. Chem. Soc.*, 119 (14) 3385-3386.

(59) Tsumaki T. (**1931**) 3, 5-DIKETOPYRAZOLIDINE DERIVATIVES. I. *Bull. Chem. Soc. Jpn.*, 6 (1) 1-8.

(60) Van Alphen J. (**1924**) The Action of Ketenes on Hydrazine Derivatives. *Recl. Des Trav. Chim. Des Pays-Bas.*, 43 (12) 823-866.

(61) Bosso C., Marsura A., and Luu-Duc C. (**1985**) Mass spectra of 1,2,4-trisubstituted 5-functionalized 2-imidazolines. *Org. Mass Spectrom.*, 20 (3) 263-264.

(62) Mustafa A., Sammour A., Kira M., Hilmy M. K., Anwar M., and Nakhla S. N. (**1965**) Beiträge zur Chemie der 3,5-Pyrazolidindione. *Arch. Pharm. (Weinheim).*, 298 (8) 516-532.

(63) Kiran K., Sarasija M., Ananda Rao B., Namratha V., Ashok D., and Srinivasa Rao A. (**2019**) Design, synthesis, and biological activity of new bis-1,2,3-triazole derivatives bearing thiophene-chalcone moiety. *Russ. J. Gen. Chem.*, 89 1859-1866.

(64) Metwally S. A., Mohamed T. A., Moustafa O. S., and El-Ossaily Y. A. (**2007**) Reactions of 4-alkylidene (arylidene)-1-phenylpyrazolidine-3,5-dione. *Chem. Heterocycl. Compd.*, 43 1131-1137.

(65) Drar A. M., Abdel-Raheem Sh. A. A., Moustafa A. H., and Hussein B. R. M. (**2023**) Studying the toxicity and structure-activity relationships of some synthesized polyfunctionalized pyrimidine compounds as potential insecticides. *Curr. Chem. Lett.*, 12 (3) 499-508.

(66) Abdel-Raheem Sh. A. A., Drar A. M., Hussein B. R. M., and Moustafa A. H. (**2023**) Some oxoimidazolidine and cyanoguanidine compounds: Toxicological efficacy and structure-activity relationships studies. *Curr. Chem. Lett.*, 12 (4) 695–704.

(67) Abdel-Raheem Sh. A. A., Kamal El-Dean A. M., Hassanien R., El-Sayed M. E. A., and Abd-Ella A. A. (**2021**) Synthesis and characterization of some distyryl-derivatives for agricultural uses. *Eur. Chem. Bull.*, 10 (1) 35-38.

(68) Kamal El-Dean A. M., Abd-Ella A. A., Hassanien R., El-Sayed M. E. A., Zaki R. M., and Abdel-Raheem Sh. A. A. (**2019**) Chemical design and toxicity evaluation of new pyrimidothienotetrahydroisoquinolines as potential insecticidal agents. *Toxicol. Rep.*, 6 (2019) 100-104.

(69) Abdel-Raheem Sh. A. A., Kamal El-Dean A. M., Zaki R. M., Hassanien R., El-Sayed M. E. A., Sayed M., and Abd-Ella A. A. (**2021**) Synthesis and toxicological studies on distyryl-substituted heterocyclic insecticides. *Eur. Chem. Bull.*, 10 (4) 225-229.

(70) Abdel-Raheem Sh. A. A., Kamal El-Dean A. M., Abdul-Malik M. A., Marae I. S., Bakhite E. A., Hassanien R., El-Sayed M. E. A., Zaki R. M., Tolba M. S., Sayed A. S. A., and Abd-Ella A. A. (**2022**) Facile synthesis and pesticidal activity of substituted heterocyclic pyridine compounds. *Rev. Roum. Chem.*, 67 (4-5) 305-309.

(71) Ahmed A. A., Mohamed S. K., and Abdel-Raheem Sh. A. A. (**2022**) Assessment of the technological quality characters and chemical composition for some Egyptian Faba bean germplasm. *Curr. Chem. Lett.*, 11 (4) 359-370.
(72) Tolba M. S., Sayed M., Kamal El-Dean A. M., Hassanien R., Abdel-Raheem Sh. A. A., and Ahmed M. (**2021**) Design, synthesis and antimicrobial screening of some new thienopyrimidines. *Org. Commun.*, 14 (4) 334-345.
(73) Abdel-Raheem Sh. A. A., Kamal El-Dean A. M., Abdul-Malik M. A., Hassanien R., El-Sayed M. E. A., Abd-Ella A. A., Zawam S. A., and Tolba M. S. (**2022**) Synthesis of new distyrylpyridine analogues bearing amide substructure as effective insecticidal agents. *Curr. Chem. Lett.*, 11 (1) 23-28.
(74) Abdel-Raheem Sh. A. A., Kamal El-Dean A. M., Abdul-Malik M. A., Abd-Ella A. A., Al-Taifi E. A., Hassanien R., El-Sayed M. E. A., Mohamed S. K., Zawam S. A., and Bakhite E. A. (**2021**) A concise review on some synthetic routes and applications of pyridine scaffold compounds. *Curr. Chem. Lett.*, 10 (4) 337-362.
(75) Abdelhafeez I. A., El-Tohamy S. A., Abdul-Malik M. A., Abdel-Raheem Sh. A. A., and El-Dars F. M. S. (**2022**) A review on green remediation techniques for hydrocarbons and heavy metals contaminated soil. *Curr. Chem. Lett.*, 11 (1) 43-62.
(76) Abdelhamid A. A., Elsaghier A. M. M., Aref S. A., Gad M. A., Ahmed N. A., and Abdel-Raheem Sh. A. A. (**2021**) Preparation and biological activity evaluation of some benzoylthiourea and benzoylurea compounds. *Curr. Chem. Lett.*, 10 (4) 371-376.
(77) Elhady O. M., Mansour E. S., Elwassimy M. M., Zawam S. A., Drar A. M., and Abdel-Raheem Sh. A. A. (**2022**) Selective synthesis, characterization, and toxicological activity screening of some furan compounds as pesticidal agents. *Curr. Chem. Lett.*, 11 (3) 285-290.
(78) Kaid M., Ali A. E., Shamsan A. Q. S., Salem W. M., Younes S. M., Abdel-Raheem Sh. A. A., and Abdul-Malik M. A. (**2022**) Efficiency of maturation oxidation ponds as a post-treatment technique of wastewater. *Curr. Chem. Lett.*, 11 (4) 415-422.
(79) Mohamed S. K., Mague J. T., Akkurt M., Alfayomy A. M., Abou Seri S. M., Abdel-Raheem Sh. A. A., and Abdul-Malik M. A. (**2022**) Crystal structure and Hirshfeld surface analysis of ethyl (3*E*)-5-(4-chlorophenyl)-3-{[(4-chlorophenyl)formamido]imino}-7-methyl-2*H*,3*H*,5*H*-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate. *Acta Cryst.*, 78 (8) 846-850.
(80) El Bakri Y., Mohamed S. K., Saravanan K., Ahmad S., Mahmoud A. A., Abdel-Raheem Sh. A. A., ElSayed W. M., Mague J. T., and Said S. G. (**2023**) 1,4,9,9-tetramethyloctahydro-4,7-(epoxymethano)azulen-5(1*H*)-one, a natural product as a potential inhibitor of COVID-19: Extraction, crystal structure, and virtual screening approach. *J. King Saud Univ. Sci.*, 35 (4) 102628.
(81) Abd-Ella A. A., Metwally S. A., Abdul-Malik M. A., El-Ossaily Y. A., AbdElrazek F. M., Aref S. A., Naffea Y. A., and Abdel-Raheem Sh. A. A. (**2022**) A review on recent advances for the synthesis of bioactive pyrazolinone and pyrazolidinedione derivatives. *Curr. Chem. Lett.*, 11 (2) 157-172.
(82) Gad M. A., Aref S. A., Abdelhamid A. A., Elwassimy M. M., and Abdel-Raheem Sh. A. A. (**2021**) Biologically active organic compounds as insect growth regulators (IGRs): introduction, mode of action, and some synthetic methods. *Curr. Chem. Lett.*, 10 (4) 393-412.
(83) Ibrahim S. M., Abdelkhalek A. S., Abdel-Raheem Sh. A. A., Freah N. E., El Hady N. H., Aidia N. K., Tawfeq N. A., Gomaa N. I., Fouad N. M., Salem H. A., Ibrahim H. M., and Sebaiy M. M. (**2024**) An overview on 2-indolinone derivatives as anticancer agents. *Curr. Chem. Lett.*, Accepted Manuscript (DOI: 10.5267/j.ccl.2023.6.005).
(84) Abdel-Raheem Sh. A. A., Kamal El-Dean A. M., Hassanien R., El-Sayed M. E. A., Sayed M., and Abd-Ella A. A. (**2021**) Synthesis and spectral characterization of selective pyridine compounds as bioactive agents. *Curr. Chem. Lett.*, 10 (3) 255-260.
(85) Fouad M. R., Shamsan A. Q. S., and Abdel-Raheem Sh. A. A. (**2023**) Toxicity of atrazine and metribuzin herbicides on earthworms (*Aporrectodea caliginosa*) by filter paper contact and soil mixing techniques. *Curr. Chem. Lett.*, 12 (1) 185–192.
(86) Shamsan A. Q. S., Fouad M. R., Yacoob W. A. R. M., Abdul-Malik M. A., and Abdel-Raheem Sh. A. A. (**2023**) Performance of a variety of treatment processes to purify wastewater in the food industry. *Curr. Chem. Lett.*, 12 (2) 431–438.
(87) Bakhite E. A., Abd-Ella A. A., El-Sayed M. E. A., and Abdel-Raheem Sh. A. A. (**2014**) Pyridine derivatives as insecticides. Part 1: Synthesis and toxicity of some pyridine derivatives against Cowpea Aphid, Aphis craccivora Koch (Homoptera: Aphididae). *J. Agric. Food Chem.*, 62 (41) 9982–9986.
(88) Bakhite E. A., Abd-Ella A. A., El-Sayed M. E. A., and Abdel-Raheem Sh. A. A. (**2017**) Pyridine derivatives as insecticides. Part 2: Synthesis of some piperidinium and morpholiniumcyanopyridinethiolates and their Insecticidal Activity. *J. Saud. Chem. Soc.*, 21 (1) 95–104.
(89) Kamal El-Dean A. M., Abd-Ella A. A., Hassanien R., El-Sayed M. E. A., and Abdel-Raheem Sh. A. A. (**2019**) Design, Synthesis, Characterization, and Insecticidal Bioefficacy Screening of Some New Pyridine Derivatives. *ACS Omega*, 4 (5) 8406-8412.
(90) Al-Taifi E. A., Abdel-Raheem Sh. A. A., and Bakhite E. A. (**2016**) Some reactions of 3-cyano-4-(*p*-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinoline-2(1*H*)-thione; Synthesis of new tetrahydroquinolines and tetrahydrothieno[2,3-*b*]quinolines. *Assiut University Journal of Chemistry (AUJC)*, 45 (1) 24-32.
(91) Abdel-Raheem Sh. A. A., Kamal El-Dean A. M., Hassanien R., El-Sayed M. E. A., and Abd-Ella A. A. (**2020**) Synthesis and biological activity of 2-((3-Cyano-4,6-distyrylpyridin-2-yl)thio)acetamide and its cyclized form. *Alger. j. biosciences*, 01 (02) 046-050.

(92) Kula K., Łapczuk A., Sadowski M., Kras J., Zawadzińska K., Demchuk O. M., Gaurav G. K., Wróblewska A., and Jasiński R. (**2022**) On the Question of the Formation of Nitro-Functionalized 2,4-Pyrazole Analogs on the Basis of Nitrylimine Molecular Systems and 3,3,3-Trichloro-1-Nitroprop-1-Ene. *Molecules*, 27 (23) 8409.
(93) Fryźlewicz A., Kącka-Zych A., Demchuk O. M., Mirosław B., Woliński P., and Jasiński R. (**2021**) Green synthesis of nitrocyclopropane-type precursors of inhibitors for the maturation of fruits and vegetables via domino reactions of diazoalkanes with 2-nitroprop-1-ene. *J. Clean. Prod.*, 292 126079.
(94) Kula K., Kącka-Zych A., Łapczuk-Krygier A., Wzorek Z., Nowak A. K., and Jasiński R. (**2021**) Experimental and theoretical mechanistic study on the thermal decomposition of 3,3-diphenyl-4-(trichloromethyl)-5-nitropyrazoline. *Molecules*, 26 (5) 1364.
(95) Sadowski M., Utnicka J., Wójtowicz A., and Kula K. (**2023**) The global and local Reactivity of C,N-diarylnitryle imines in [3+2] cycloaddition processes with trans-β-nitrostyrene according to Molecular Electron Density Theory: A computational study. *Curr. Chem. Lett.*, 12 (2) 421-430.
(96) Kula K., and Zawadzińska K. (**2021**) Local nucleophile-electrophile interactions in [3+2] cycloaddition reactions between benzonitrile *N*-oxide and selected conjugated nitroalkenes in the light of MEDT computational study. *Curr. Chem. Lett.*, 10 (1) 9-16.
(97) Domingo L. R., Kula K., Rios-Gutierrez M., and Jasinski R. (**2021**) Understanding the participation of fluorinated azomethine ylides in carbenoid-type [3+2] cycloaddition reactions with ynal systems: A molecular electron density theory study. *J. Org. Chem.*, 86 (18) 12644-12653.
(98) Kula K., and Sadowski M. (**2023**) Regio-and stereoselectivity of [3+2] cycloaddition reactions between (*Z*)-1-(anthracen-9-yl)-N-methyl nitrone and analogs of trans-β-nitrostyrene on the basis of MEDT computational study. *Chem. Heterocycl. Compd.*, 59 (3) 138–144.
(99) Kula K., Nagatsky R., Sadowski M., Siumka Y., and Demchuk O. M. (**2023**) Arylcyanomethylenequinone Oximes: An Overview of Synthesis, Chemical Transformations, and Biological Activity. *Molecules*, 28 (13) 5229.
(100) Zawadzińska K., Ríos-Gutiérrez M., Kula K., Woliński P., Mirosław B., Krawczyk T., and Jasiński R. (**2021**) The participation of 3,3,3-trichloro-1-nitroprop-1-ene in the [3+2] cycloaddition reaction with selected nitrile *N*-oxides in the light of the experimental and MEDT quantum chemical study. *Molecules*, 26 (22) 6774.
(101) Kula K., Dobosz J., Jasiński R., Kącka-Zych A., Łapczuk-Krygier A., Mirosław B., and Demchuk O. M. (**2020**) [3+2] Cycloaddition of diaryldiazomethanes with (*E*)-3,3,3-trichloro-1-nitroprop-1-ene: An experimental, theoretical and structural study. *J. Mol. Struct.*, 1203 127473.
(102) Zawadzińska K., Gadocha Z., Pabian K., Wróblewska A., Wielgus E., and Jasiński R. (**2022**) The First Examples of [3+2] Cycloadditions with the Participation of (*E*)-3,3,3-tribromo-1-nitroprop-1-ene. *Materials*, 15 (21) 7584.
(103) Boguszewska-Czubara A., Kula K., Wnorowski A., Biernasiuk A., Popiołek Ł., Miodowski D., Demchuk O. M., and Jasiński R. (**2019**) Novel functionalized β-nitrostyrenes: Promising candidates for new antibacterial drugs. *Saudi Pharm. J.*, 27 (4) 593-601.
(104) Boguszewska-Czubara A., Lapczuk-Krygier A., Rykala K., Biernasiuk A., Wnorowski A., Popiolek L., Maziarka A., Hordyjewska A., and Jasiński R. (**2016**) Novel synthesis scheme and in vitro antimicrobial evaluation of a panel of (*E*)-2-aryl-1-cyano-1-nitroethenes. *J. Enzyme Inhib. Med. Chem.*, 31 (6) 900-907.
(105) Zawadzińska K., Gaurav G. K., and Jasiński R. (**2022**) Preparation of conjugated nitroalkenes: short review. *Sci. Rad*., 1 69-83.
(106) Woliński P., Kącka-Zych A., Mirosław B., Wielgus E., Olszewska A., and Jasiński R. (**2022**) Green, one-pot synthesis of 1,2-oxazine-type herbicides via non-catalyzed Hetero Diels-Alder reactions comprising (2E)-3-aryl-2-nitroprop-2-enenitriles. *J. Clean. Prod.*, 356 131878.
(107) Ríos-Gutiérrez M., Domingo L. R., and Jasiński R. (**2023**) Unveiling the high reactivity of experimental pseudodiradical azomethine ylides within molecular electron density theory. *Phys. Chem. Chem. Phys.*, 25 (1) 314-325.