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One-Pot Synthesis of Benzopyrano-Pyrimidine Derivatives Catalyzed by P-Toluene Sulphonic Acid and Their Nematicidal and Molecular Docking Study

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Abstract: A cost-effective and environmentally benign benzopyrano-pyrimidine derivative synthesis has been established with the condensation of different salicylaldehyde derivatives, piperidine/morpholine with malononitrile, in the presence of a catalyst containing p-toluene sulphonic acid (PTSA) at 80 °C temperature. This procedure offers a new and enriched approach for synthesizing benzopyrano-pyrimidine derivatives with high yields, a straightforward experimental method, and short reaction times. The synthesized compounds were investigated for their nematocidal activity, and the result shows that among the four compounds, compounds **4** and **5** showed strong nematocidal activity against egg hatching and J2s mortality. The nematocidal efficacy of the compounds might be due to the toxicity of chemicals which are soluble in ethanol. The nematocidal effectiveness was directly related to the concentration of ethanolic dilutions of the compounds, i.e., the maximum treatment concentration, the higher the nematocidal action, or the higher the mortality and egg hatching inhibition. In the present study, with support from docking analysis, the relation between chemical reactivity and nematocidal activity of compound **4** was inferred.

Keywords: benzopyrano-pyrimidine; malononitrile; piperidine; PTSA; molecular docking

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1. Introduction

Heterocyclic compounds have been prepared from many methods which contain significant biological activities in multicomponent reactions [1–5]. Selectivity, atom economy, rapid reaction times, and ability are critical characteristics of multicomponent reactions. Multicomponent reactions have recently been shown to be a significant development for synthesizing structurally varied chemical collections of the drug since the products are formed in a single step, and the variety can be achieved by simply moving each component [6]. Nitrogen-containing heterocyclic pyrimidines and their fused derivatives serve an essential function in medicinal chemistry and have been employed as drug development scaffolds [7–15]. Benzopyrano-pyrimidine is an important pharmacore that exhibits anti-thrombotic, anti-inflammatory, anti-aggregating, anti-platelet, and analgesic properties [16–20]. Many benzopyrano-pyrimidines contain anti-tumor activity and cytotoxic activity against cancer cell lines [18]. Some quinazolines and pyrimidine derivatives [21] are shown in various activities in Figure 1.

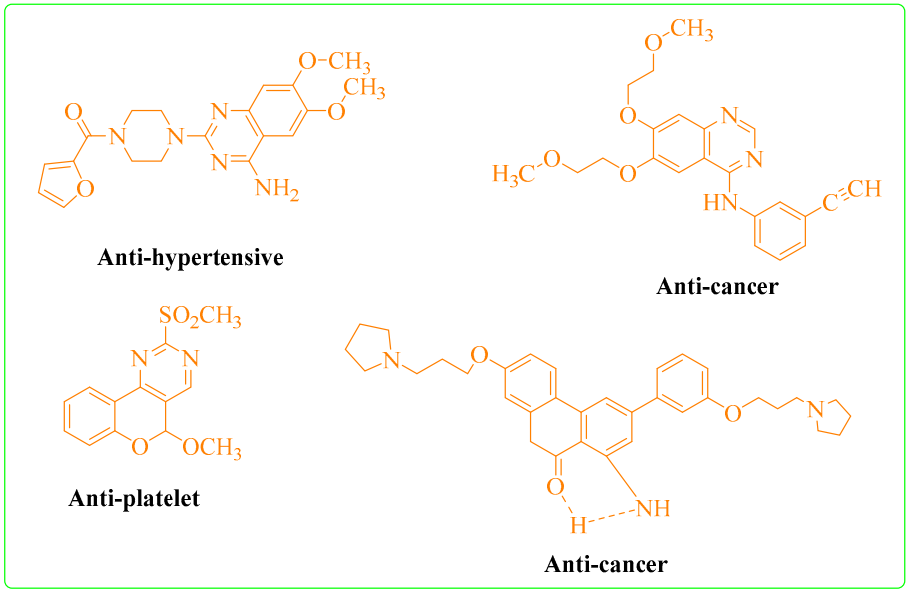


Figure 1. Biologically important derivatives of pyrimidine.

In the last decades, benzopyrano-pyrimidine one has been prepared via a three-component reaction of malononitrile, salicylaldehyde, and piperidine/morpholine by use of a catalytic amount of $LiClO_4$ [22], $Na_2MoO_4{\cdot}2H_2O$ [23], $[Bim]BF_4$ [24], Fe_3O_4 and SBA-15 [25], Fe(II)-benzoyl thiourea complex bound silica nanoparticles [Fe(II)-BTU-SNPs] [26], TiO_2–SiO_2 [27], p-toluenesulfonic acid supported by polystyrene in a solvent-free sonochemical multicomponent synthesis [28], and Brønsted acidic ionic liquid [29]. Solid acid catalysts have long been used in the oil refining industry, for example, in cracking processes and chemical manufacturing. In contrast, a substantial variety of acid-catalyzed reactions, including Friedel–Crafts reactions, esterification, hydration, and hydrolysis, are still catalyzed by conventional acids such as $AlCl_3$, H_2SO_4, and so on [30]. Chemical reactions employing traditional acids, on the other hand, are frequently linked with issues such as catalyst waste, corrosion, high toxicity, the use of huge volumes of catalyst, and separation and recovery challenges. Similarly, prolonged reaction times, elevated temperatures, high solvent costs, and the difficulty of separating conventional acids from the product are all disadvantages of using them as homogeneous catalysts [31] in laboratory trials for benzopyrano-pyrimidines synthesis. Additionally, organocatalysts such as proline and its derivatives and chiral phosphoric acids can be used to selectively synthesize heterocyclic compounds due to their achiral or chiral nature. Besides that, they have a number of advantages, not only due to their synthetic range, but also due to lower price. The absence of metals in organocatalysts is undeniably advantageous from both a green chemistry and economic standpoint. However, the high catalyst loading, the time and cost associated with removing and recycling excess catalyst from the reaction mixture, as well as the relatively young field, all work against widespread use of organocatalysts [32,33]. Consequently, a more efficient, ecologically friendly, and practical method of production of benzopyrano-pyrimidines was considered.

The use of p-toluene sulphonic acid (PTSA) as a solid catalyst for benzopyrano-pyrimidines synthesis via a three-component reaction in ethanol at 80 °C has been recommended as a non-explosive, non-toxic, and easily accessible option. After forming benzopyrano-pyrimidine derivatives, various spectroscopic techniques, including X-ray crystallographic, ^{1}H NMR, ^{13}C NMR, FT-IR, elemental analysis, and mass spectrophotometry, were employed to confirm the structure of the synthesized compounds. The 2-(4-(piperidine-1-yl)-*5H*-chromeno[2,3-d]pyrimidin-2-yl) phenol (**2**) structure was further confirmed by single-crystal X-ray diffraction with good conformity with earlier reports [32]. The synthesized compounds were also investigated for their nematocidal activity. The

results show that compounds **4** and **5** showed strong nematocidal activity against egg hatching and J2s mortality among the four compounds. The nematocidal efficacy of the compounds might be due to the toxicity of chemicals which are soluble in ethanol. The nematocidal activity of the compounds in ethanolic dilutions was directly proportional to their concentration, i.e., the maximum treatment concentration, the higher the nematocidal action, or the more significant the mortality and egg hatching inhibition. In the current work, molecular docking of the active compound obtained from the experimental investigation was used to understand the mechanistic approach of non-bonding interactions with receptors and determine active amino acids' participation in receptors. The computer-generated 3D structure of ligands is docked into a receptor structure in various orientations, conformations, and sites via molecular docking. A molecular recognition strategy can help with medicine innovation and medicinal chemistry [34].

2. Results and Discussion

A small series of benzopyrano-pyrimidine derivatives were synthesized in this paper using p-toluene sulphonic acid in ethanol under reflux conditions. This approach outperforms other available synthetic methods in terms of yield, reaction timings, product purity, and catalyst stability. These synthetic benzopyrano-pyrimidine derivatives possess different applicability and are well-matched with several other functional groups.

2.1. Chemistry

Based on FT-IR, NMR (^{1}H & ^{13}C), and mass spectra analyses, the structure of all synthesized benzopyrano-pyrimidine derivatives was determined and found to be in good agreement with the anticipated structure. Furthermore, the spectroscopic data of compounds **2** and **4** matches those described in the literature quite well [27,28]. The reaction occurs at the carbonyl and hydroxy moieties of one mole of salicylaldehyde, as evidenced by the FT-IR spectra, which reveal that the produced molecule has no aldehyde group frequency. Furthermore, the entire compound showed a characteristic peak for the group, appearing at approximately 3418, 2857.4, 1619, and 1600.83 cm^{-1}, indicating the formation of benzopyrano-pyrimidine derivatives. The saturated proton in each synthesized molecule resonance had a sharp singlet at approximately δ 4.35 ppm, at around δ 9.0–12.5 ppm with a broad peak accounted to the-OH proton of a benzene ring, and the benzene ring proton displayed a multiplet at around 6.98–8.75 ppm in the ^{1}H NMR spectra of the synthesized compounds. ^{13}C NMR spectra display signals at about δ 119–165, which have been shown aromatic carbon, with a peak display at around δ 155–159 to -C=N and 161–165 to –C-O of pyrano moiety. Similarly, the signal resonated at δ 22–50 has been ascribed to a saturated carbon. The mass analysis of the prepared series was very suitable in conformity with the design structure.

2.2. Crystal Structure

Compound **2** crystallizes in the asymmetric unit (ASU) in the monoclinic P21/n space group (Figure 2). All of the bonds in the ASU have a considerable range of bond lengths, *viz*. N2–C1 (1.476(3) Å), N2–C5 (1.452(2) Å), N2–C6 (1.373(3) Å), N1–C6 (1.336(2) Å), N1–C16 (1.341(3) Å), N3–C15 (1.329(2) Å), N3–C16 (1.316(3) Å), O2–C14 (1.398(3) Å), O2–C15 (1.359(3) Å) and O1–C18 (1.313(4) Å). The molecule is non-planar with a dihedral angle of 33.17° between the mean planes of C1–N2–C5 and C7–C6–N1. Meanwhile, the dihedral angle between the mean planes of N3–C16–N1 and C9–C10–C11 is 22.80°.

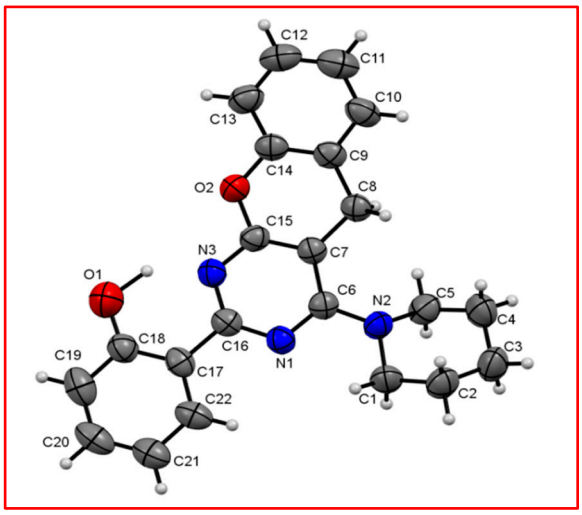
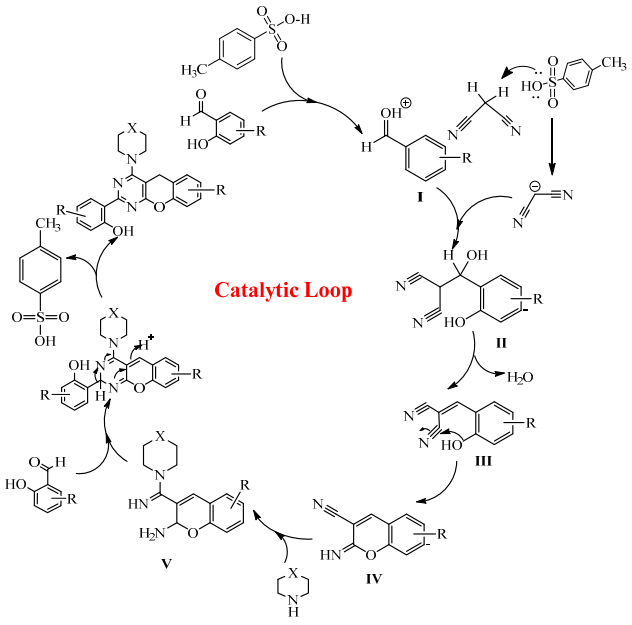


Figure 2. The asymmetric unit of compound **2** with atom labeling and displacement ellipsoids are drawn at the 50% probability level.

2.3. Mechanism

A tentative mechanism pathway for the p-toluene sulphonic acid (PTSA)-catalyzed synthesis of the benzopyrano-pyrimidine derivative has been described based on the literature [28] as shown in Scheme 1. First, the reaction is started by protonating the carbonyl group from the p-toluene sulphonic acid catalyst, which produces an active electrophilic intermediate **I** and makes the carbonyl carbon more electrophilic, lowering its pKa value. Further, the conjugate base of the catalyst generated in situ in the reaction mixture acts as a nucleophile which abstracts a proton from the active methylene carbon of malononitrile. This step facilitates the formation of a tetrahedral intermediate **II**. In the next step, elimination of the water molecule forms intermediate **III**. Then, intermolecular cyclization occurs by attaching the phenolic group of salicylaldehyde to the cyanide group, and intermediate **IV** is obtained. In the next step, piperidine attaches onto intermediate **IV**, and intermediate **V** is formed. In the last step, the second molecule of salicylaldehyde attaches to intermediate **V**. Finally, the formation targets the benzopyrano-pyrimidine derivatives with the removal of the catalyst (Scheme 1).



Scheme 1. A tentative mechanism for the synthesis of benzopyrano-pyrimidine derivatives.

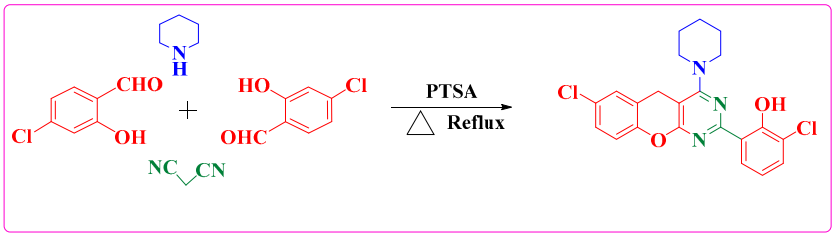
2.4. Optimization of Reaction Conditions

Firstly, the focus was on optimizing the reaction conditions for the current protocol concerning the reaction temperature, the amount of catalyst, and the choice of solvent in our study, and selecting a suitable catalyst for a chosen model reaction using salicylaldehyde, malononitrile, and hetero/aromatic aldehyde from various catalysts to provide the best possible reaction condition for the synthesis of the benzopyrano-pyrimidine derivatives.

2.4.1. Effect of Different Solvent

In the presence of p-toluene sulphonic acid, the effect of other solvents on the reaction rate and yield of the product was investigated. Solvents such as $CHCl_3$, CH_3NO_2, CH_2Cl_2, and CH_3CN were unsatisfactory. In water, the reaction did not proceed. In methanol, DMF, and THF, the reaction completed in 8 h. In ethanol, the reaction produced the best results, the minimum time for completion, and gave a good yield. The results are shown below in Table 1.

Table 1. Effect of different solvents on the reaction [a].



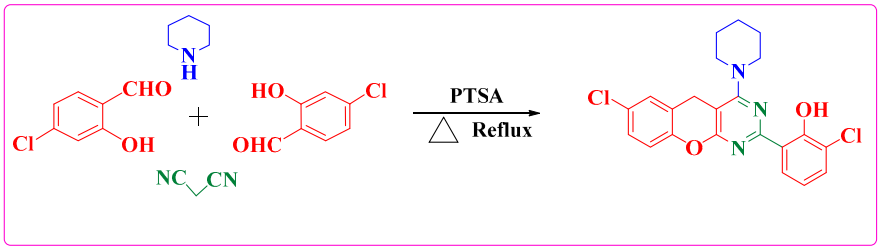
Entry [a]	Solvent	Condition	Time (h) [b]	Yield [c]
1	H_2O	Reflux	24	Trace
2	CH_3CN	Reflux	10	32
3	CH_3COCH_3	Reflux	8	55
4	$CHCl_3$	Reflux	8	35
5	CH_3NO_2	Reflux	8	45
6	CH_2Cl_2	Reflux	8	25
7	THF	Reflux	8	66
8	DMF	Reflux	7	55
9	MeOH	Reflux	8	73
10	EtOH	Reflux	40 min	95

[a] Reaction of 4-chloro-salicylaldehyde (1 mmol) with malononitrile (1 mmol) and piperidine (1 mmol) in the presence of 10 mol% PTSA as a catalyst. [b] Reaction progress monitored by TLC. [c] Isolated yield.

2.4.2. Effect of Different Catalysts

There are many catalysts used in the optimization of model reactions. To emphasize the efficiency of p-toluene sulphonic acid-catalyzation compared to other catalysts, the reaction was carried out with various catalysts such as pyridine, $AlCl_3$, $FeCl_3$, $ZnCl_2$, I_2, NH_4OAc, and NaOAc. Without catalysts, the reaction occurs for a long time and has a low yield. It is observed that the reaction performed with I_2 and NH_4OAc was complicated after a long reaction time with a 72–80% yield. The model reaction was also carried out in $FeCl_3$ and $AlCl_3$ with less reaction time but low yield, and the product obtained a minimal amount. The reaction was completed with zinc chloride in a short time and with a moderate yield. The model reaction was completed in a short reaction time when p-toluene sulphonic acid was used with a high yield (Entry 9) (Table 2).

Table 2. The influence of different catalysts on the model reaction under thermal solvent-free conditions.



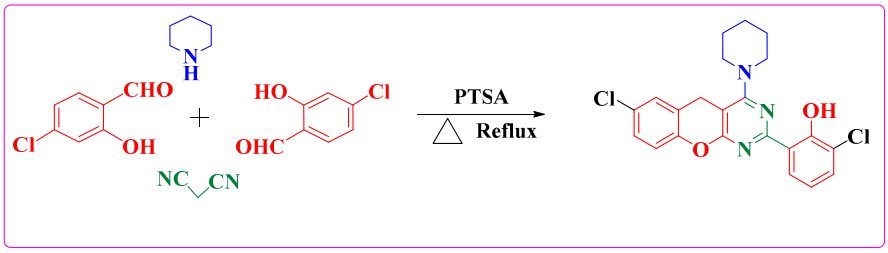
Entry [a]	Catalyst	Time (h) [b]	Yield [c]
1	None	23	25
2	Pyridine	3.5	50
3	$FeCl_3$	3	40
4	$AlCl_3$	2.5	35
5	I_2	12	72
6	NH_4OAc	8	75
7	NaOAc	6	80
8	$ZnCl_2$	5	60
9	PTSA	40 min	95

[a] Reaction of 4-chloro-salicylaldehyde (1 mmol) with malononitrile (1 mmol), piperidine (1 mmol) in the presence of 10 mol% PTSA as a catalyst. [b] Reaction progress monitored by TLC. [c] Isolated yield.

2.4.3. Effect of Catalyst Loading

The effect of loading catalyst was tested in the model reaction. In optimization, we analyzed the reaction by varying the loading amount of the catalyst in the model reaction from 2 to 10 mol%. Finally, the results show that 10 mol% of the catalyst was sufficient to give a better yield (entry 5) (Table 3).

Table 3. Effect of catalyst loading on the reaction.



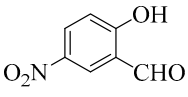
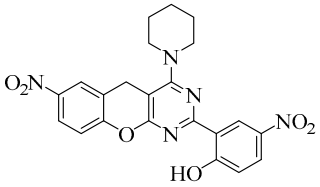
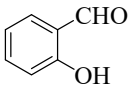
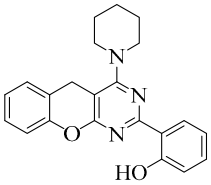
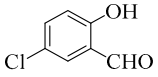
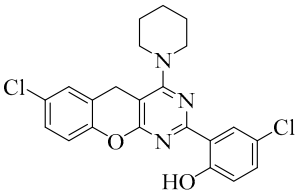
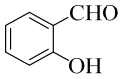
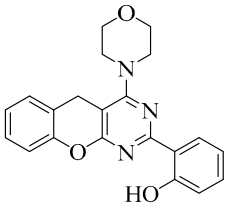
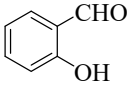
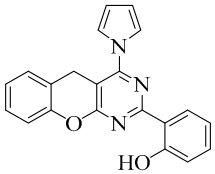
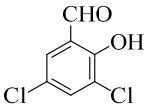
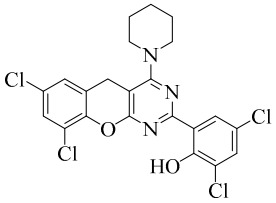
Entry [a]	Catalyst (Mol%)	Time (Min) [b]	Yield [c]
1	2	2 h	60
2	3	1.5 h	75
3	5	1.0 h	80
4	10	40	88
5	10	40 min	95

[a] Reaction of 4-chloro-salicylaldehyde (1 mmol) with malononitrile (1 mmol), piperidine (1 mmol) in the presence of 10 mol% PTSA as a catalyst. [b] Reaction progress monitored by TLC. [c] Isolated yield.

2.4.4. Catalytic Reaction

With these encouraging results in hand, we turned to explore the scope of the reaction using different aromatic aldehydes (2a–g), malononitrile, and piperidine as substrates under the optimized reaction conditions (Table 4). It was observed that the aromatic aldehydes with electron-donating and electron-withdrawing groups reacted successfully to furnish the final products **1–6** in good yields (Table 4).

Table 4. Synthesis of benzopyrano-pyrimidine derivatives using PTSA at 80 °C temperature.

Entry	Reactant (1)	Reactant (2)	Product	Time (min)	Yield (%)	M.P.
1.		Piperidine		40	92	260–262
2.		Piperidine		40	90	170–172
3.		Piperidine			95%	255–256
4.		Morpholine		40	90	220–222
5.		Piperidine		40	90	230–232
6.		Piperidine		40	93	170

2.4.5. Catalyst Recycling

Effective catalyst recovery from the reaction mixture is the most important aspect for determining its usability for practical applications, from an environmental and economic standpoint. As a result, catalyst recycling studies were performed to establish the degree of recyclability of our catalytic system (Figure 3). As a model reaction, the reaction of 4-chloro-salicylaldehyde, malononitrile, and piperidine in the presence of 10 mol% PTSA was used. After the reaction was completed, the catalyst was recovered by extracting the mixture with ethyl acetate and then filtering it. After that, the catalyst was washed with ethyl acetate and reused in consecutive cycles. In ethanol, the catalyst maintained its activity for at least five reaction cycles, demonstrating excellent catalytic performance with a product yield of over 95%.

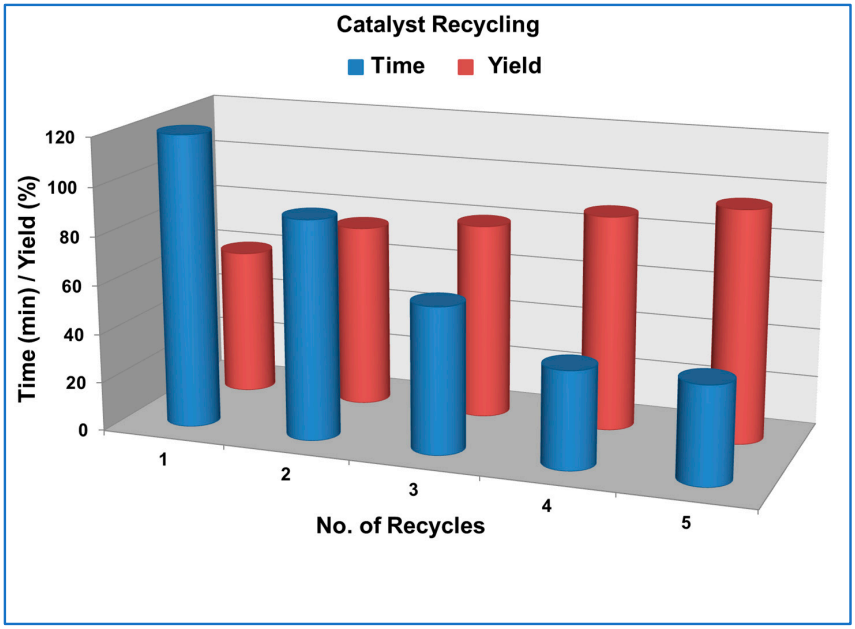


Figure 3. Recycling data of PTSA catalyst.

2.5. Nematicidal Activity

The data analysis in Table 4 indicates that mortality of juveniles of *Meloidogyne javanica* was recorded (8) in absolute alcohol (control). However, all the concentrations of each diluted compound, i.e., **2**, **3**, **4**, and **5**, significantly impacted mortality. Second stage (J2) juvenile mortality was directly correlated to the concentrations and exposure period. The highest mortality (98.9%) was observed in 100% concentration of compound **4** after 72 h of exposure time. In contrast, the lowest mortality was found in compound 2 (7.6%) at 12.5% concentration after the exposure period of 24 h (Table 5).

Table 5. Effect of different dilutions of organic chemicals on the mortality of juvenile root-knot nematode *Meloidogyne javanica* in vitro.

Compounds	Exposure Period (Hours)	Percent Mortality in Different Concentrations					Regression Equation
		100%	50%	25%	12.2%	Control	
2	**24**	72 (69.5)	60 (56.5)	51 (46.7)	15 (7.6)	8.00	Y = 17.19x − 13.91
	48	79 (77.1)	65 (61.9)	58 (54.3)	18 (10.8)	8.00	Y = 18.93x − 14.37
	72	83 (81.5)	79 (77.1)	70 (67.3)	23 (16.3)	8.00	Y = 20.78x − 12.30
3	**24**	80 (78.2)	68 (65.2)	53 (48.9)	17 (9.7)	8.00	Y = 19.59x − 16.77
	48	86 (84.7)	74 (71.7)	63 (59.7)	20 (13.0)	8.00	Y = 21.21x − 16.21
	72	91 (90.2)	85 (83.6)	76 (73.9)	29 (22.8)	8.00	Y = 22.52x − 11.86
4	**24**	90 (89.1)	68 (65.2)	55 (51.0)	30 (23.9)	8.00	Y = 20.35x − 13.61
	48	93 (92.3)	86 (84.7)	75 (72.8)	35 (29.3)	8.00	Y = 22.4x − 9.78
	72	99 (98.9)	90 (89.1)	81 (79.3)	55 (51.0)	8.00	Y = 21.99x − 0.71
5	**24**	86 (84.7)	65 (61.9)	50 (45.6)	26 (19.5)	8.00	Y = 19.58x − 14.80
	48	91 (90.2)	77 (72.8)	63 (59.7)	34 (28.2)	8.00	Y = 20.9x − 10.92
	72	95 (94.4)	82 (80.4)	67 (64.1)	39 (33.6)	8.00	Y = 21.96x − 9.78

Each value is an average of three replicates.

In vitro nematicidal activity of compounds was displayed as an LC50 value with 95% confidence limits. The effect of organic chemicals on probit output and LC 50 was calculated. As the concentrations of the compounds increased from 12.5% to 100%, juvenile mortality also increased. The toxins of compound **4** convert nematode natality into mortality with LC50 values 27.21, 17.91, and 11.89 percent after 24, 48, and 72 h of exposure time, respectively. The findings indicated that compound **4** was highly toxic to mortality of *M. javanica* at 100% concentration of 72 h time duration. Compounds **5**, **3**, and **2** followed. After 24, 48, and 72 h of exposure, compound **2** showed the least toxicity in terms of nematode mortality, with LC50 values of 42.97, 34.36, and 24.44, respectively (Table 6).

Table 6. Nematicidal activity of different concentrations of compounds against juveniles of *Meloidogyne javanica*.

Compounds	Exposure Time (Hours)	LC_{50} Value in Percent (95% CL)
2	24	42.97
	48	34.36
	72	24.44
3	24	35.10
	48	27.97
	72	19.62
4	24	27.21
	48	17.91
	72	11.89
5	24	31.79
	48	21.93
	72	18.70

Similarly, dilutions of each compound were also considered effective against *M. javanica* egg hatching. After 7 days of exposure, compound **4** was the most reactive of the four compounds, whereas compound **2** was the least effective at a 12.5 percent dilution. Compound **2** had the lowest amount of hatching (95.8, 89.7, 78.8, and 54.8%). On the other hand, maximum egg hatching of *M. javanica* second-stage juveniles (J2) was shown by compound **4** (100, 96.0, 87.6, and 62.7%) at different dilutions such as 100%, 50%, 25%, and 12.5% concerning their control (ethanol). As per data analysis, the maximum percent inhibition in *Meloidogyne javanica* egg hatching was indicated by compound **4** (100%) at 100% concentration (Table 7). Alternatively, the minimum hatchability of J2s was revealed by compound **2** (54.8%) at 12.5% diluted form after seven days of time duration (Table 7).

Table 7. Effect of different ethanolic dilutions of various compounds on the egg hatching of *Meloidogyne javanica* in vitro after 7 days.

Compounds	Number of Larvae Hatched in Different Dilutions				
	100%	**50%**	**25%**	**12.5%**	**Control**
2	22 (95.8%)	55 (89.7%)	113 (78.8%)	241 (54.8%)	534 (0.00%)
3	16 (97.0%)	41 (92.3%)	87 (83.7%)	227 (57.4%)	534 (0.00%)
4	0 (100%)	21 (96.0%)	66 (87.6%)	199 (62.7%)	534 (0.00%)
5	9 (98.3%)	27 (94.9%)	78 (85.3%)	214 (59.9%)	534 (0.00%)

Each value is an average of three replicates, DW = Distilled Water (control). The value of percent inhibition in egg hatching over control is given in parentheses.

Conclusions reached that compounds **4** and **5** showed strong nematocidal activity against egg hatching and J2s mortality among the four synthesized compounds. The

nematocidal efficacy of the synthesized compounds might be due to the toxicity of compounds that are soluble in ethanol. The previous findings showed that salicylaldehyde derivatives and other chemicals possess nematicidal potency against most damaging soil-borne pathogens, i.e., Phyto parasitic nematodes [35–37]. In the current in vitro testing, the ethanolic dilutions of compounds **2**, **3**, **4**, and **5** showed significant nematotoxicity or nematocidal potentiality against juvenile mortality and egg hatching of *M. javanica*. The four ethanolic doses of the synthesized compounds were the most efficient in lowering egg hatching and increasing mortality. Results analysis revealed that the nematocidal efficacy was proportionate to the concentration of compounds in ethanolic dilutions, i.e., the maximum treatment concentration, the higher the nematocidal action, or greater the mortality and egg hatching inhibition [38].

In vitro mortality investigation showed that compound **4** exhibited the highest nematocidal potency against the survival of J2s of *M. javanica* after 72 h of exposure time. Compound **4** had the least LC50 values compared to other compounds (**5**, **3**, and **2**) at 24, 48, and 72 hrs of exposure. The mortality of the second stage (J2) juveniles increases with the increase of all compound concentrations, along with exposure time initiated from 24 to 72 h. Related results were described by [39], who report that aromatic aldehydes such as salicylaldehyde, Phthaldehyde, and cinnamic aldehydes actively demonstrated nematocidal activity against the root-knot nematode, *M. incognita* in in vitro study. So, it can be concluded that the toxicity of synthesized compounds toward nematodes depends on the concentrations of treatment and the exposure period (Figure 4).

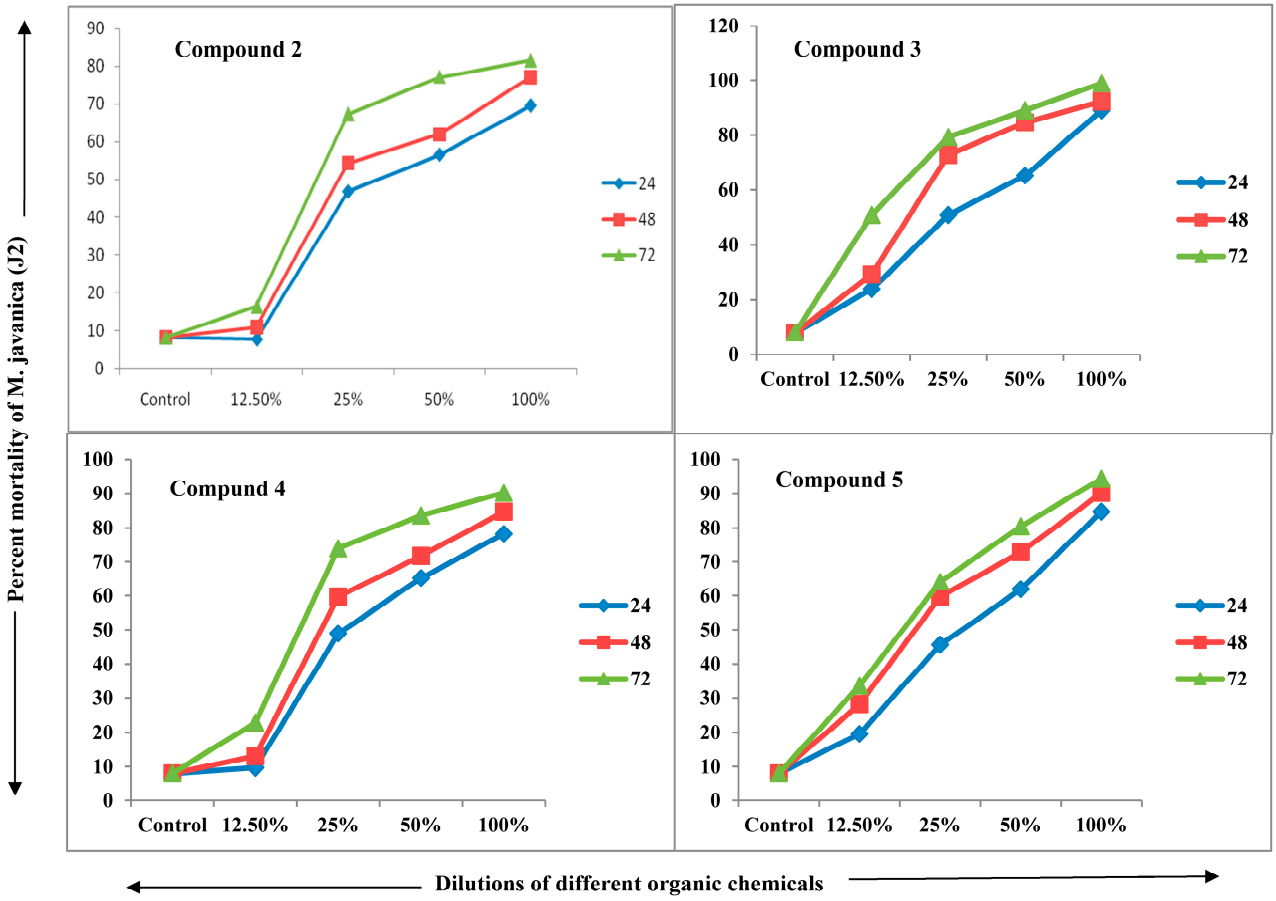


Figure 4. Regression lines show a linear relationship between different dilutions of organic chemicals against juvenile mortality *M. javanica* at another exposure period.

2.6. Docking Analysis

The crystal structure of yeast V1-ATPase in the autoinhibited form of Saccharomyces cerevisiae was chosen for the docking investigation, and docking was conducted to identify the non-bonding contacts between the compound that showed good nematocidal activity in this study and the receptor. Compound **4** was docked between β-strand β-21 and α-helix α4, containing 284–287 and 357–360 residues, in a docking experiment (Figure 5). The best docked posed established a hydrophobic pocket at the receptor site with residues PHE538, ILE541, LEU235, PRO233, PRO540, and TRP542 adjacent to compound **4** with binding energy (8.3420 kcal/mol).

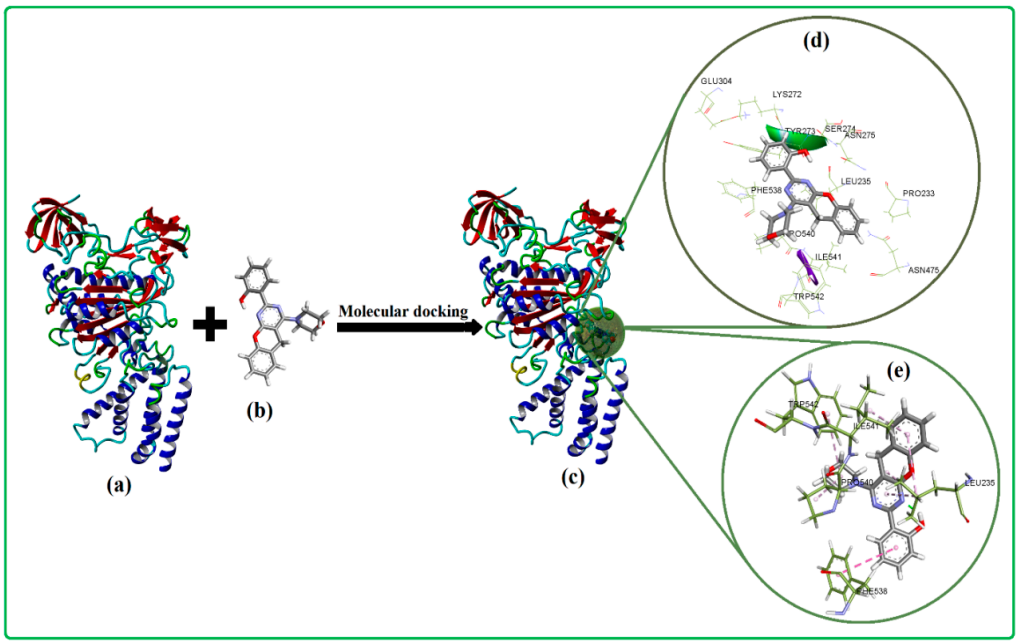


Figure 5. Molecular docking of the (**a**) receptor (PDB: 5D80) with (**b**) the compound **4**, (**c**) the docked compound into active site shown in the circle, (**d**) involvement of various amino acids interacting with compound **4**, and (**e**) compound **4** interacts with the receptor, forming non-bonding contacts with the aromatic and non-aromatic skeletons.

The envelope of these active amino acids that interact with compound **4** is positioned in the amino acids pocket in the proper orientation, to establish close contact with the receptor and stop plant-parasitic nematodes from spreading. Furthermore, apart from hydrophobic amino acids, hydrophilic amino acids are present around the ligands such as LYS 272, TYR 273, SER 274, ASN 275, ASN 475, and GLU 304 are also involved in various interactions such as van der walls, pi-pi-T-shaped, pi-alkyl, and so on, as shown in Figure 5. These interactions boosted the compound's stability as well as its biological activity.

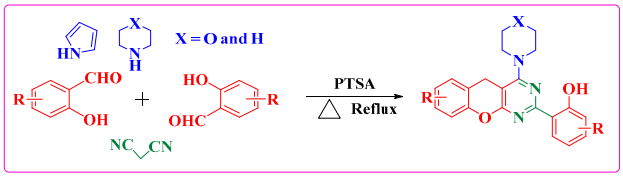
3. Materials and Methods

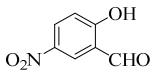
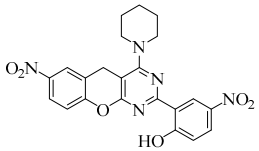
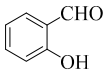
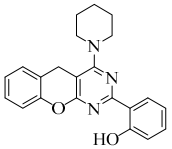
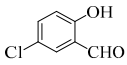
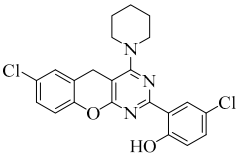
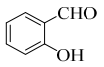
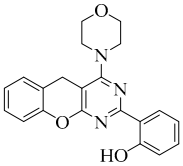
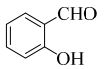
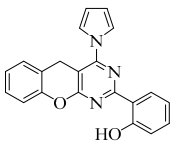
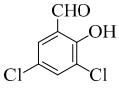
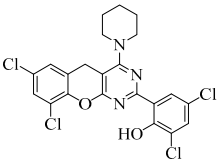
All chemicals were purchased from Merck and Sigma-Aldrich (Mumbai, India) as "synthesis grade" and used without further purification. Kofler apparatus (Nageman, Germany) was used to determine melting points and are uncorrected. A Carlo Erba analyzer model 1108 (Milan, Italy) was used to analyze elemental analysis (C, H, N). The Shimadzu IR-408 instrument (Shimadzu Corporation, Kyoto, Japan) recorded the IR spectra, and the values were set in cm^{-1}. For the ^{1}H NMR and ^{13}C NMR spectra, a Bruker Avance-II 400 MHz instrument (Bruker Instruments Inc., Billerica, MA, USA) was used, and the spectra run in DMSO-d_6 with TMS as an internal standard, and the J values were measured in Hertz (Hz). Chemical shifts were reported in ppm (δ) relative to TMS. A JEOL D-300 mass spectrometer was used to record the Mass spectra. Thin-layer chromatography (TLC)

glass plates (20 × 5 cm) were coated with silica gel G (Merck) (Darmstadt, Germany) and exposed to iodine vapors to check the homogeneity as well as the progress of the reaction.

*3.1. General Procedure for the Synthesis of Benzopyrano-Pyrimidines Derivatives (**1**–**6**)*

A mixture of salicylaldehyde **1** (1 mmol), malononitrile **2** (1 mmol), and piperidine/morpholine (1 mmol) was added to p-toluene sulphonic (10 mol%). The reaction mixture was refluxed and stirred at 80°C for the required time. The completion of the reaction was monitored by thin-layer chromatography (TLC) using n-hexane and ethyl acetate (8:2). After completing the reaction as indicated by TLC, the reaction mixture was treated with ice-cold water. The mixture was filtered to collect the crystal. Separation of the catalyst was completed by filtration and the resulting solution was extracted with ethyl acetate. The aqueous organic layer was washed with brine, poured onto anhydrous Na_2SO_4, and filtered under reduced pressure. The pure product obtained was crystallized with ethanol chloroform to afford pure crystal (Scheme 2).



Substituents (R)	Product
	
	
	
	
	
	

Scheme 2. Synthetic pathway for the synthesis of benzopyrano-pyrimidines derivatives **1**–**6**.

3.2. Spectral Data of Synthesized Compounds

Spectroscopic and elemental analysis data for the heterocyclic compounds (**1**–**6**) synthesized and reported in the literature are given as Supplemental Materials.

3.3. X-ray Crystallographic Studies

Additional information to the structure of compound **2** is specified in Table 8.

Table 8. Crystallographic data and experimental details compound **2**.

Parameters	Compound 2
Empirical Formula	C_{22} H_{21} N_3O_2
Formula weight	359.42
Crystal size/mm	0.30 × 0.36 × 0.40
Crystal system	Monoclinic
Unit cell dimensions	a = 9.9377 (2) Å b = 15.8917 (3) Å c = 12.1806 (3) Å α = γ = 900 β = 108.7810
Space group	*P*21/*n*
Z	4
Temperature (K)	293
Wavelength (Å)	0.71073 Å
Volume (Å^3)	1821.22 (7)
Density (g cm^{-3})	1.311
μ/mm^{-1}	0.086
F(000)	760
Measured reflections	44244
Independent reflections	4015 (Rint = 0.112)
Observed reflections [$I \geq 2\sigma(I)$]	2667
Goodness-of-fit on F2	1.149
Radiation type	MoKα
h, k, l max	12, 20, 15
Final R indices	*R*1 = 0.078
[$I \geq 2\sigma(I)$]	w*R*2 = 0.280

3.4. Inoculum Maintenance

The pure culture of root-knot nematode, *Meloidogyne javanica*, was multiplied on the brinjal plant under the greenhouse of the Department of Botany, Aligarh Muslim University, Aligarh (India). Infected roots were separated from the adhering soil, washed gently in tap water, and kept in a distilled water tray (DW). The root-knot nematode species *M. javanica* identification was carried out based on the technique of the perineal patterns [40]. The roots were cut into small segments, and egg masses were handpicked from the root for hatching purposes. These egg masses were transferred to Petri dishes (40 mm) containing DW at 27 ± 2 °C in a BOD incubator. The suspension containing the juveniles was collected after the fifth day of hatching, and fresh DW was added. The concentration of freshly hatched J2 juveniles of *M. javanica* was standardized as per the requirement for in vitro testing.

3.5. In Vitro Nematicidal Activity Bioassays

3.5.1. Hatching Test

Five new and uniform-size egg masses of *M. javanica* were handpicked from the infected roots of brinjal. The collected egg masses were transferred to Petri dishes (40 mm) containing 10 mL of each synthesized compound in different concentrations (100%, 50%, 25%, and 12.5%). Distilled water containing egg masses served as a control. Each treatment, including the control, had three replicates. All the Petri dishes were incubated in a BOD (biological oxygen demand) incubator at 28 °C for seven days. After seven days, hatched

juveniles in the treated and control samples were recorded using a counting dish with the help of a stereomicroscope.

3.5.2. Mortality Test

For mortality, 0.4 mL of DW containing 100 juveniles of *M. javanica* was transferred into the Petri dishes containing 9.6 mL of synthesized compounds of four different concentrations (100%, 50%, 25%, and 12.5%). Petri dishes containing juveniles in DW were considered as the control. Each treatment, including the control, was replicated three times. All the Petri dishes were kept at 28 °C in BOD. The number of dead juveniles was counted with the help of a counting dish under a stereomicroscope at different time intervals (24, 48, and 72 h). The mortality of the juveniles was confirmed by transferring immobilized juveniles into fresh DW water for 1 h and observing if any movement was shown by nematode. If there was no mobility, then they were considered dead. Probit analysis was used to compute the LC50 values for all treatments based on percent mortality data and concentration [41].

The following formula was used to compute the percent inhibition in egg hatching or juvenile mortality:

$$\% \text{ inhibition or mortality} = \left(\frac{C_0 - T\alpha}{C_0}\right) \times 100\%$$

where, in terms of egg hatching, $T\alpha$ = number of juveniles hatched in each concentration of the compound dilutions, C_0 = number of juveniles hatched in the control. In the case of mortality, $T\alpha$ = number of live nematodes after 24, 48, and 72 h of exposure, C_0 = number of juveniles living in the control.

3.6. Docking Study

Molecular docking between compound **4** and the V1-ATPase crystal structure receptor downloaded from the *RCSB* Protein Data Bank was performed with YASARA software [42] using the dock_run.MCR module that was available in YASARA-Structure. Initially, the receptor's PDB file was imported into YASARA, and water molecules and ions from the receptor were removed from the structure. The missing hydrogen atoms and residues were added to the receptor. One of the multiple receptor structures was saved for docking studies. Chem Draw was used to sketch the 2D structure of compound **4**, which was then transformed to a 3D structure by Chem3D before being optimized using molecular mechanics using the MM+ force field and saved in sd format for the docking study. YASARA View was used to illustrate the best dock pose from the docking experiment, which was then converted to PDB format for Molecular graphics by a BIOVIA Discovery Studio Visualizer (Discovery Studio Visualizer, version 16.1.0; Dassault Systemes, BIOVIA Corp., San Diego, CA, USA).

4. Conclusions

The protocol provides not only a high yield of products and a shorter reaction time but also high purity, mild reaction conditions, operational simplicity, a cleaner reaction profile, increased reaction rates, and a simple workup approach. We hope that this synthetic protocol will provide a more feasible alternative to the other available methods for synthesizing benzopyrano-pyrimidine. Compounds **4** and **5** had a significant nematocidal effect on egg hatching and J2s mortality. The nematocidal efficacy of the compounds might be due to the toxicity of chemicals which are soluble in ethanol. The analysis revealed that the nematocidal efficacy was proportionate to the concentration of the compounds in ethanolic dilutions, i.e., the maximum treatment concentration, the greater the mortality or, the higher the nematocidal action, as well as egg hatching inhibition. For the investigation of close contacts with active amino acids, the molecular docking of compound **4** against the 3D structure of V1-ATPase obtained from Saccharomyces cerevisiae was employed.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal12050531/s1, Characterization data for compounds (**1**–**6**) and copies of NMR spectra (^{1}H and ^{13}C) for two new compounds (**3**–**4**). Figure S1: ^{1}H NMR Spectra of Compound **3**; Figure S2: ^{13}C NMR Spectra of Compound **3**; Figure S3: ^{1}H NMR Spectra of Compound **4**; Figure S4: ^{13}C NMR Spectra of Compound **4**.

Author Contributions: Supervision, formal analysis, writing—review and editing, M.P.; conceptualization, methodology, writing—original draft preparation, M.A. (Mohammad Azeem), A.A.K., K.M., A.A.; software, validation, visualization, M.A. (Mahboob Alam), Y.A.; investigation, resources, M.A. (Mahboob Alam), S.F., M.A.S. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Data obtained during this study are included in the main text and Supplementary Materials.

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Conflicts of Interest: The authors declare no conflict of interest.

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