Research Article

SOHAG JOURNAL OF SCIENCES

https://doi.org/10.21608/sjsci.2024.248555.1148

Synthesis and Characterization of Some Novel Indole-2-One-Coumarin Hybrids

Omyma A. Abd Allah[1*], Ehab S. M. Elkhayat[2], Amr H. Moustafa[1,3] and Alaa A. Fahmy[1]

[1] *Chemistry Department, Faculty of Science, Sohag University, Sohag 82524, Egypt*
[2] *Pharmacognosy Department, Faculty of Pharmacy, Al-Azhar University, Assiut branch, Egypt*
[3] *Faculty of Science, King Salman International University, Ras Sudr, Sinai 46612, Egypt*
**Email: omymatif66@yahoo.com, omaima.abdelatef@science.sohag.edu.eg*

Received: 17th November 2023 **Revised:** 6th January 2024 **Accepted:** 9th January 2024
Published online: 20th February 2024

Abstract: Hybridization has recently emerged as a promising strategy for discovering new drugs. Therefore, given the important bioactivity of isatins as well as coumarins, several new hybrids based on the isatin and coumarin nuclei were proposed, synthesized, and characterized in this study. Using a simple and modified dehydration reaction, 3-hydroxy-3-[2-oxo-2-(2-oxo-2H-chromen-3-yl)ethyl] indolin-2-one was used as the starting material for the preparation of 3-(2-oxo-2-(2-oxo-2H-chromen-3-yl)ethyli-dene) indolin-2-one (**2**) with high yield compared to the reported procedures. In this study, compound 2 served as a building block in preparing the targeted spiro[indole-2-one-3,4'-pyrimidin-2-one]-coumarin hybrids, in simple and eco-friendly one-pot reactions. The Infrared (IR), nuclear magnetic resonance (^{1}HNMR and ^{13}CNMR) spectroscopic data, and elemental analyses were used to determine the compositional assignments of these prepared hybrids. Here the antimicrobial effect of four products **3-5** was determined on only two fungal strains: Penicillium notatum and Alternaria solani. The results showed no effect of these compounds on the fungi used. It was very evident that the tested fungi strains were resistant. Accordingly, further studies must be conducted on a wider range of fungal strains in the future to get more effective data in this field.
Keywords: Isatin, coumarin, hybrid, chalcone, pyrimidine.

1. Introduction

Isatin is a naturally occurring compound with low molecular weight found in many plants, human blood, and tissues [1]. It is a non-peptide compound found to be a prevalent component in various dyes, agrochemicals, and pharmaceuticals [2, 3]. Isatins and spiroindoles are more striking moieties in organic and medicinal chemistry and also have many biological activities, including the antibacterial [4], antiviral [5], anticonvulsant [6], antinflammatory [7] and antifungal [8]. Coumarin along with its derivatives also represents an important class of anti-inflammatory, antioxidant, and analgesic drugs [9]. The Sunitinib, nintedanib, warfarin, and hymecromone drugs, which are based on isatin and coumarin moieties, have recently been approved for the treatment of several diseases [10, 11]. Nowadays, hybridization is the contemporary trend in the drug design area [12, 13]. It is the fusion of two or more active pharmaceutical ingredients within one new molecular framework. It has been found to have a higher affinity as a polydrug. The reported results on isatin hybrids and our ongoing work in the synthesis of medical coumarin and aza compounds [14-19] encouraged us to synthesize some new isatin-coumarin hybrids. The structures of the new materials were interpreted based on IR, ^{1}H-NMR, ^{13}C-NMR, and elemental analyses.

2. Materials and methods

2.1. Materials

Sigma-Aldrich (purity 99%) and Merck Millipore (purity 99%) are the providers of the chemical reagents used. The Kofler instrument was used to determine the melting points of the prepared compounds. FT-IR-ALPHBROKER-Platinum-ATR spectrometer was used to record the infrared spectra, which are given as cm^{-1} using the attenuated total reflection method. Using a Bruker Bio Spin AG spectrometer at 400MHz the (^{1}H and^{13}C-NMR) nuclear magnetic resonance spectroscopy were recorded in DMSO-d6 and $CDCl_3$.Chemical shifts (δ) were given in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard with δ=0. The Perkin-Elmer CHN analyzer was used for elemental analyses.

2.2. Methods

2.2.1. Synthesis of 3-(2-Oxo-2-(2-oxo-2*H*-chromen-3-yl) ethylidene)indolin-2-one (2) [20, 21]

In a round flask, conc. HCl (31 mL) was added to a solution of compound **1** (1 g, 0.003 mol) in ethanol (15 mL) at 35ºC and set to stand for 24 hrs. The final unrefined material was separated from the mixture by filtration as orange crystals. The purified compound was obtained by recrystallizing the crude solid compound from benzene, which after that was verified by its melting point and spectral analyses. 0.90g (94%) yield. IR (υ_{max}, cm^{-1}): 3157 (NH), 3075, 3026 (CH $_{arom.}$), 2959, 2896 (CH $_{aliph}$), 1710 (C=O $_{coumarin\ and\ keton}$), 1657 (C=O $_{amide}$), 1604, 1553 (C=C), 1323(C-N), 1186cm^{-1} (C-

O).^{1}H-NMR (DMSO-d_6) δ ppm: 10.68 (s, 1H, NH disappeared in D_2O), 8.82 (s, 1H, CH-1' $_{arom}$), 8.33- 8.31 (d, 1H, CH $_{arom}$), 8.02-8.00 (d, 1H, CH $_{arom}$), 7.85 (s, 1H, CH $_{coumarin}$), 7.81-7.77 (t, 1H, CH $_{arom}$), 7.51-7.49 (d, 1H, CH $_{arom}$), 7.48-7.44 (t, 1H, CH $_{arom}$), 7.40-7.37 (t, 1H, CH $_{arom}$), 7.02-6.99 (t, 1H, CH $_{arom}$), 6.91-6.89 (d, 1H, CH $_{arom}$). ^{13}C- NMR (DMSO-d_6) δ ppm: 188.11 (C=O), 168.99 (C=O), 159.05, 155.27, 148.96, 145.73, 136.87, 135.37, 133.88, 131.44, 127.80, 127.63, 125.70, 125.56, 122.21, 120.55, 118.85, 116.75, 110.84. Anal. Calc. for $C_{19}H_{11}NO_4$(317.30): C,71.9; H, 3.47; N, 4.4 %. Found: C, 71.82; H, 3.44; N, 4.38.

2.2.2. Synthesis of compounds (3-5) using the general method:

The aromatic aldehyde namely, salicaldehyde, 2-methoxybenzaldehyde, and/or 3-nitrobenzaldehyde (0.003 mol), compound **2** (1 g, 0.003 mol) were dissolved in acetic acid (glacial) (20 mL). One hour was selected as a suitable time to heat the mixture under reflux. Next, urea (0.18 g, 0.003mol) was added to the mixture used throughout the process and allowed to reflux for an additional 3 hrs. After converting the reactants into products, they were adjusted at room temperature and precipitated by adding them to an ice bath (100 mL). The refined 2-oxo-spiro[indole-3,4'-pyrimidin-2'-one]-5′-[(2-oxo-chromen-3-yl) derivatives **3-5** were obtained via recrystallizing the crude solids from a suitable solvent.

2.2.2.1. 2-Oxo-spiro[indole-3,4'-pyrimidin-2'-one]-5′-[(2-oxo-2H-chromen-3-yl)-5′-oxo]-6′-[2-hydroxy phenyl] (3).

Crystalized from methanol as a brown powder, yield 1.08g (72 %), m.p.228-230℃. IR (υ_{max}, cm^{-1}): 3408 (OH and NH), 3090 (CH $_{arom}$), 2926 (CH $_{aliph}$), 1778 (C=O $_{coumarin}$), 1719 (C=O $_{Ketone}$),1663 (C=O $_{amide}$), 1610, 1559 (C=C), 1186 cm^{-1} (C-O). ^{1}H-NMR (DMSO-d_6) δ ppm: 10.80 (s,1H, NH $_{isatin}$ disappeared in D_2O), 8.88 (s, 1H, OH disappeared in D_2O), 8.38-8.36 (d, 1H, CH $_{arom}$), 8.07-8.05 (d, 1H, CH $_{arom}$), 7.90 (s, 1H, CH-4 $_{coumarin}$), 7.86-7.82 (t, 1H, CH $_{arom}$), 7.57-7.55 (d, 1H, CH $_{arom}$), 7.52-7.49 (d and t, 2H, CH $_{arom}$), 7.45-7.42 (t, 2H, CH_{arom}), 7.24 (s, 2H, NH $_{pyrimidone}$ disappeared in D_2O), 7.07-7.04 (t, 2H, CH $_{arom}$), 6.96-6.94 (d, 2H, CH $_{arom}$). DEPT 135 NMR (DMSO-d_6) δ ppm: 148.97, 142.32, 135.39, 133.90, 131.45, 129.64, 127.83, 127.63, 125.58, 124.41, 122.23, 116.76, 110.85. Anal. Calc. for $C_{27}H_{17}N_3O_6$ (479.45): C, 67.64; H, 3.57; N, 8.76 %. Found: C, 67.55; H, 3.51; N, 8.66.

2.2.2.2. 2-Oxo-spiro[indole-3,4'-pyrimidin-2'-one]-5′-[(2-oxo-2H-chromen-3-yl)-5′-oxo]-6′-(2-methoxy phenyl) (4a)

Crystallized from methanol as brownish-orange powder, yield 1.01g (65%), m.p.229-231℃. IR(υ_{max} ,cm^{-1}): 3184, 3159 (NH), 3078 (CH $_{arom.}$), 2898 (CH $_{aliph.}$), 1778 (C=O $_{coumarin}$), 1715 (C=O $_{Ketone}$), 1658 (C=O $_{amide}$), 1607 (C=N), 1557 (C=C), 1222 (C-N), 1190cm^{-1} (C-O). ^{1}H-NMR(DMSO-d_6) δ ppm: 10.75 (s, 1H, NH $_{isatin}$ disappeared in D_2O), 8.83 (s, 1H, NH disappeared in D_2O), 8.34-8.32 (d, 1H, CH $_{arom.}$), 8.02-8.00 (d, 1H, CH $_{arom.}$), 7.85 (s, 1H, CH $_{coumarin}$), 7.81-7.77 (t, 1H, CH $_{arom.}$), 7.52- 7.37 (2d and 3t, 5H, CH $_{arom.}$), 7.03- 6.99 (t, 2H, CH $_{arom.}$), 6.91-6.89 (d, 2H, CH $_{arom.}$), 3.74 (s, 1H, NH disappeared in D_2O), 3.26 (s, 3H, OCH_3). DEPT 135 NMR (DMSO-d6)δ ppm: 148.94, 135.37,133.86, 132.95, 132.45, 131.42, 127.79, 127.60, 125.57, 122.22, 121.05, 116.74, 110.85, 67.37 (OCH_3). Anal. Calc. for $C_{28}H_{19}N_3O_6$ (493.48): C, 68.15; H, 3.85; N, 8.5 %. Found: C, 68.11; H, 3.83; N, 8.44.

2.2.2.3. 2-Oxo-spiro[indole-3,4'-pyrimidin-2'-one]-5′H,5′-[(2-oxo-2H-chromen-3-yl)-5′-oxo]-6′-(2-methoxy phenyl) (4b)

It is insoluble in methanol and grained as a brown material from DMF, 0.46g(30 %) yield and m.p.229-231℃. IR (υ_{max} ,cm^{-1}): 3188, 3159 (NH), 3083 (CH $_{arom.}$), 2964, 2898 (CH $_{aliph.}$), 1776 (C=O $_{coumarin}$), 1715 (C=O $_{Ketone}$), 1660 (C=O $_{amide}$), 1608 (C=N), 1558 (C=C), 1222(C-N), 1190 cm^{-1}(C-O). ^{1}H-NMR (DMSO-d_6) δ ppm: 10.81 (s, H, NH $_{isatin}$ disappeared in D_2O), 8.89 (s, 1H, CH $_{coumarin}$), 8.39-8.37 (d, 1H, CH $_{arom.}$), 8.07-8.06 (d, 1H, CH $_{arom.}$), 7.90 (s, 1H, NH $_{pyramid-2-one}$), 7.87-7.83 (t, 1H, CH $_{arom.}$), 7.55-7.53 (d, 2H, CH $_{arom.}$), 7.51-7.46 (t, 2H, CH $_{arom.}$), 7.44-7.42 (t, 2H, CH $_{arom.}$), 7.08-7.04 (d and t, 2H, 2CH $_{arom.}$), 6.97-6.95 (d, 1H, CH $_{arom.}$), 3.79 (s, 1H, CH-5 $_{pyrimid-2-one}$), 3.34 (s, 3H, OCH_3). Anal. Calc. for $C_{28}H_{19}N_3O_6$ (493.48): C, 68.15; H, 3.85; N, 8.51%. Found: C, 68.09; H, 3.85; N, 8.4.

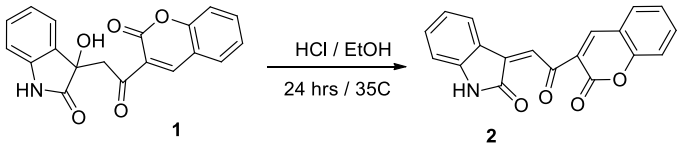
2.2.2.4. 2-Oxo-Spiro[indoline-3,4'-pyrimidin]-5'-[(2-oxo-2H-chromen-3-yl)-5′-oxo]-6'-(3-nitrophenyl) (5)

Crystallized from methanol as brownish-orange powder, yield 0.95g (85%), m.p. 239-241℃. IR (υ_{max}, cm^{-1}): 3354, 3186 (NH), 3063 (CH $_{arom}$), 2958, 2923 (CH $_{aliph}$), 1777 (C=O $_{coumarin}$), 1713 (C=O $_{ketone\ and\ amide}$), 1608, 1558 (C=C), 1528, 1390 (NO_2), 1328 (C-N), 1182 cm^{-1} (C-O-C).^{1}H-NMR($CDCl_3$)δ ppm: 8.51 (s, 1H, CH $_{coumarin}$), 8.47-8.45 (d, 1H, CH $_{arom}$), 8.1-7.94 (t, 1H, CH $_{arom}$), 7.63-7.60 (d and t, 3H, 3CH $_{arom}$), 7.38 (s, 1H, NH $_{isatin}$ disappeared in D_2O), 7.35-7.33 (d, 1H, CH $_{arom}$), 7.32 (s, 1H, NH $_{pyrimidin-2-one}$ disappeared in D_2O), 7.30-7.26 (d and t, 3H, CH $_{arom}$), 6.99-6.95 (d and t, 2H, CH $_{arom}$), 6.77-6.75 (d, 1H, CH $_{arom}$), 0.1 (s, 1H, NH disappeared in D_2O). DEPT 135 NMR ($CDCl_3$) δ ppm: 148.20, 144.14, 134.72, 133.28, 130.19, 127.21, 125.09, 122.79, 116.94, 114.59, 109.92, 99.98. Anal. Calc. for $C_{27}H_{16}N_4O_7$ (508.45): C, 63.78; H, 3.15; N, 11.02 %. Found: C, 63.70; H, 3.12; N, 11.00.

3. Results and Discussion:

3.1. Chemistry

The ß-hydroxy carbonyl compound, 3-hydroxy-3-[2-oxo-2-(2-oxo-2H-chromen-3-yl)ethyl]indolin-2-one (**1**) [20] was intended to be a starting compound for the production of various types of isatin-coumarin hybrids. Therefore, compound **1** was subjected to a dehydration reaction to generate the chosen α,ß-unsaturated carbonyl compound, 3-(2-oxo-2-(2-oxo-2H-chromen-3-yl)ethylidene)indolin-2-one (**2**) [20, 21]. This reaction was carried out under a modified condition, by keeping compound **1** in concentrated hydrochloric acid for 24 hrs at a temperature at 35ºC. This method was more productive than other reported methods [20, 21] (*cf.* scheme 1 and experimental). According to the literature, concentrated hydrochloric acid was first used as a dehydrating agent in this reaction. While the dehydration step of compound **1** was performed earlier, under other conditions such as acetic acid/ hydrochloric acid or ethanol /diethylamine.

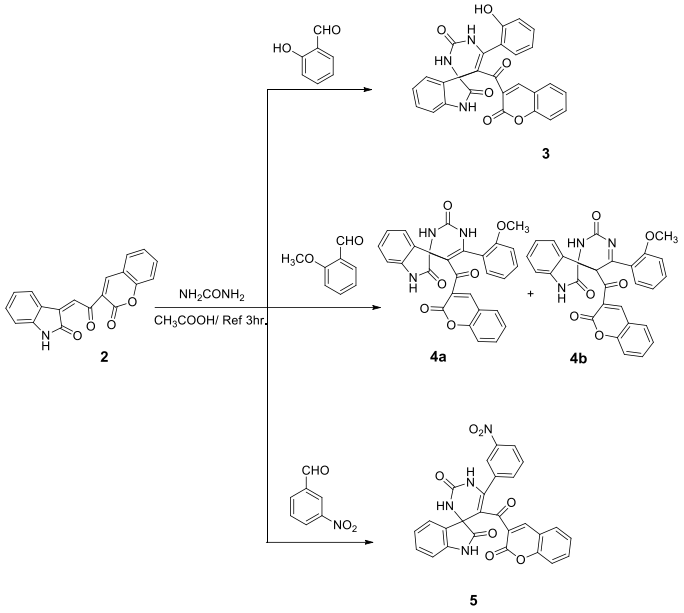


Scheme 1

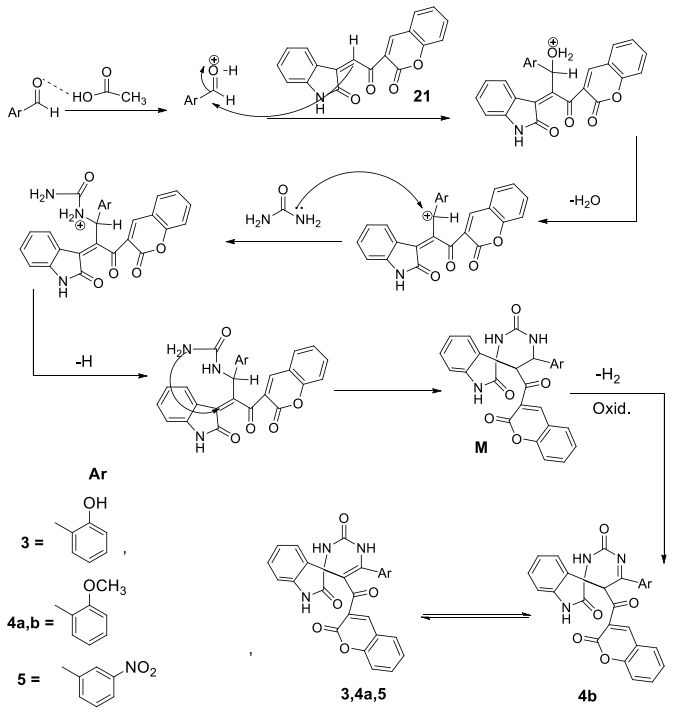
The IR spectrum pointed to the vanishing of the OH group band and the appearance of the characteristic bands for NH and C=O of coumarin, ketone, and amide groups at υ_{max} 3157, 1710, and 1657cm^{-1} respectively. ^{1}HNMR spectral analysis reflected the absence of the CH_2 protons related to compound **1** and the presence of definite signals at δ 10.68 ppm of NH, δ 8.82 and 7.85 ppm of CH chalcone and CH-4 coumarin protons (*cf.* experimental).

The reactivity of the α,ß-unsaturated carbonyl group -CO-CH=C-of the compound **2** prompted us to study its one-pot condensation reaction with urea and various aromatic aldehydes in search of the 2-oxoindole-spiro pyrimidine-coumarin hybrids. These compounds constitute a major structural element in many natural products [22]. Compound **2** was reacted with equimolar amounts of 2-hydroxy-benzaldehyde (salicaldehyde) and urea in boiling acetic acid to afford the 2-oxo-spiro[indole-3,4'-pyrimidin-2'-one]-5′-[(2-oxo-2H-chromen-3-yl)- 5′-oxo]-6′-[2-hydroxyphenyl**] (3)** (*cf.* scheme 2). The chemical structure of this product was decided with IR, ^{1}HNMR, ^{13}CNMR, and elemental analyses. The IR spectrum showed different bands at υ_{max} 3408 cm^{-1} of OH and NH groups, 1778, 1719, and 1663 cm^{-1} of three C=O coumarin, ketone, and amide groups, respectively. ^{1}H-NMR spectrum reflected the formation of three singlet signals at δ 10.80, 7.24 ppm representing three NH protons of isatin and prymidin-2-one rings and δ 8.88 ppm of OH proton, these signals disappeared in D_2O. While the signal at δ 7.90 ppm of CH-4 coumarin (*cf.* experimental). The steps of this reaction move forward under the effect of the acetic acid through a condensation reaction between the aldehyde C=O group, with both the CH group at chalcone and an NH_2 group at urea by removing a water molecule. Next, a nucleophilic addition reaction of the free NH_2 group occurred at C-3 of the 2-oxo-indole at the non-separated intermediate M, followed by spontaneous removal of the H_2 molecule *via* air oxidation to form 2-oxo-spiro[indole-3,4'-pyrimidin-2'-one]-5′-[(2-oxo-2H-chromen-3-yl)- 5′-oxo] derivative as shown at scheme 3.

Under the same previous reaction condition, compound **2** was reacted also with *o*-methoxy-benzaldehyde and urea producing two isomers, 2-oxo-spiro[indole-3,4'-pyrimidin-2'-one]-5′-[(2-oxo-2H-chromen-3-yl)-5′-oxo]-6′-(2-methoxy phenyl)(**4a**) and 2-oxo-spiro[indole-3,4'-pyrimidin-2'-one]-5′H,5′-[(2-oxo-2H-chromen-3-yl)-5′-oxo]-6′-(2-methoxy phenyl) **(4b)** (*cf.* scheme 2). These two isomers have been separated from each other based on their solubility in boiling methanol. The IR spectrum of compounds **4a** and **4b** showed the characteristic NH bands at υ_{max} 3184, 3188 cm^{-1} and C=O bands of coumarin, ketone, and amide ranged at 1778-1776, 1715,1660-1658 cm^{-1}, respectively (*cf.* experimental). ^{1}HNMR spectrum of compound **4a** showed distinct individual characteristic signals, at υ_{max} 10.75, 8.83, and 3.74 ppm, disappeared in D_2O of the three NH protons at isatin and



Scheme 2



Scheme 3

pyrimidine rings. While ^{1}HNMR spectrum of compound **4b** showed the formation of two individual beaks at δ 10.81 and 7.90 ppm of only two NH protons at isatin and pyrimidine rings respectively. The CH-5 of the pyrimidine ring appeared at δ 3.79 ppm, which confirmed the formation of the second isomer. DEPT 135 NMR and elemental analyses supported the suggested structures (*cf.* experimental). Whereas the reaction of compound **2** with *m*-nitrobenzaldehyde and urea under the same reaction condition as the previous one gave the 2-oxo-spiro [indoline-3,4'-pyrimidin]-5'-[(2-oxo-2H-chromen-3-yl)-5′-oxo]-6'-(4-nitro phenyl) (**5**) as only product

(*cf.* scheme 2). The output of compound **5** was more than compounds **3** and **4a,b**. This was the result of the electron-withdrawing effect of the NO_2 group at *m*-nitrobenzaldehyde compared to the electron-donating effect of the OH and OCH_3 groups in *o*-hydroxy (methoxy) benzaldehyde (*cf.* experimental). According to the spectroscopic analyses, the IR spectrum showed the NH band at υ_{max} 3186 cm^{-1} and the C=O bands of coumarin, ketone, and amide at υ_{max} 1777 and 1713 cm^{-1}.While the NO_2 group appeared as two characteristic bands at υ_{max} 1528 and 1390 cm^{-1}. From the ^{1}HNMR spectrum, the characteristic signals of the CH-4 proton of coumarin appeared at δ 8.51ppm, and signals of NH protons of isatin and pryimide-2-one at δ 7.38, 7.32, and 0.19 ppm, which disappeared in D_2O (*cf.* experimental).

3.2. Biological Activity

Adopting the agar plate diffusion assay [23], the synthesized compounds **3-5** were tested as anti-microbials. Analysis of the results showed that none of these compounds was effective against the examined fungal strains *P. notatum* and *A. solani*.

4. Conclusion

In this work, novel isatin-coumarin and spiro[indole-2-one-3,4'-pyrimidin]-coumarin hybrids were prepared using a simple one-pot eco-friendly method. The spiro[indole-3,4'-pyrimidin] - coumarin hybrid **5** was formed in greater yield than compounds **3** and **4a,b**, under the electron accepting effect of NO_2 group at *m*-nitrobenzaldehyde compared to the electron-donating effects of the *o*-OH(OCH_3) benzaldehyde. The new products were recognized using infrared (IR), nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectroscopy as well as elemental analyses. Compounds **3-5** have no activity against the fungal strains *P. notatum* and *A. solani*. It was very clear that the tested strains were resistant.

CRediT authorship contribution statement:

Omyma A. Abd Allah: Conceptualization, Methodology, Investigation, Writing-review and editing, Supervision, Project administration. Ehab S. M. Elkhayat: Methodology, Investigation, Formal analysis, Writing-original draft preparation. Amr H. Moustafa: Formal analysis, Investigation. Alaa A. Fahmy: Methodology, Formal analysis, Writing-original draft. All authors have read and agreed to the published version of the manuscript.

Data availability statement

Authors can confirm that all relevant data are included in the essay and its supplementary data files.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] N. Hamaue, M. Minami, M. Hirafuji, M.Terado, M. Machida, N. Yamazaki, M. Yoshioka, A. Ogata, K. Tashiro, *CNS Drug Rev*. 5 (1999) 331.

[2] F.A. Khan, A. Maalik, T. Noor, A.Zaidi, U. Farooq, S.M. Bukhari, *Trop. J. Pharm. Res.*, 14 (2015) 1937.

[3] B.V. Silva, *J. Braz. Chem. Soc.*, 24 (2013) 707.

[4] X.-M.Zhang, H. Guo, Z.-S. Li, F.-H. Song , W.-M.Wang , H.-Q. Dai, L.-X.Zhang , J.-G. Wang, *Eur. J. Med. Chem.*, 101 (2015) 419.

[5] T. Wang, O. B. Wallace, Z. Zhang, H. Fang, Z. Yang, B. A. Robinson, T. P. Spicer, Y. F. Gong, W. S. Blair, P. Y. Shi, P. F. Lin, M. Deshpande, N.A. Meanwell, J. F. Kadow, *Bioorg, Med. Chem. Lett.*, 29 (2019) 1423.

[6] C. Xie, L.-M.Tang, F.-N.Li, L.-P.Guan, C.-Y. Pan, S.-H. Wang, *Med. Chem. Res.*, 23 (2014) 2161.

[7] E.V., B.Ghosh, N.G.J. Richards, et al., *J. Enzym. Inhib. Med. Chem.*, 31 (2016) 1520.

[8] A. A. Raj, R. Raghunathan, M. R. Sridevi, K. N. Raman, *Bioorg. Med. Chem.*, 11 (2003) 407.

[9] KC. Fylaktakidou, DJ. Hadjipavlou-Litina , KE. Litinas, DN. Nicolaides, *Curr Pharm Des*., 10 (2004) 3813.

[10] F. Rahim, F. Malik, H. Ullah, A. Wadood, F. Khan, , M.T. Javid, M.Taha, W. Rehman, A.U. Rehman, K.M. Khan, *Bioorg. Chem*., 60 (2015) 42.

[11] X. L. Hu, C.Gao, Z. Xu, M. L.Liu, L. S. Feng, G.D. Zhang, *Curr Top Med Chem.*, 18 (2018) 114.

[12] H. Singh, J.V. Singh, M.K. Gupta, A.K. Saxena, S. Sharma, K. Nepali, P.M.S. Bedi, *Med. Chem. Lett*., 27 (2017) 3974.

[13] M. Sanduja, J. Gupta, H. Singh, P.P. Pagare, A Rana, *J Saudi Chem. Soc.*, 24 (2020) 251.

[14] O. A. Abd Allah, *Il Farmaco*, 55 (2000) 641.

[15] A. M. El Sayed, O. A. Abd Allah, *Phosphorus, Sulfur and Silicon*, 170 (2001) 75.

[16] A.B.A.G. Ghattas, H.M. Moustafa, O. A. Abd Allah, A. A. Amer; *Synthetic Communications*, 31 (2001) 2447.

[17] O. A. Abd Allah, Nassr L. A. E., *Monatshefte Fur Chemi*, 146 (2016) 1.

[18] O. A. Abd Allah, *Phosphorus, Sulfur and Silicon* 178 (2003) 1115.

[19] O. A. Abd Allah, *Chemistry of Heterocyclic Compounds*, 8 (2005) 1256.

[20] R.A. Kusanur, M. Ghate, M.V. Kulkarni, *J. Chem. Sci.* 116 (2004) 265.

[21] E. A. Fayed, R. R. Ezz Eldin, A. B. M. Mehany, A. H. Bayoumi, Y. A. Ammar, *Journal of Molecular Structure*, 1234 (2021) 130159.

[22] C.V. Galliford and K.A. Scheidt, *J. Org. Chem*., 72 (2007) 1811.

[23] E. Elkhayat, R. Edrada, R. Ebel, V. Wray, R. Van Soest, S. Wiryowidagdo, H. M. Mohammed, W. E. Muller, P. Proksch, *J. Nat. Prod*., 67 (2004) 1809.