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ORIGINAL PAPER

Microwave-assisted green synthesis, antimicrobial activity, and drug-likeness of novel isoindolinone derivatives

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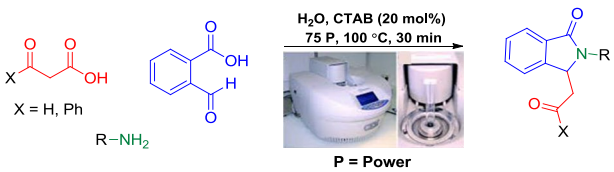
Abstract

An efficient and green microwave method has been developed for the synthesis of novel isoindolinone derivatives with good yields. The framework of these derivatives was constructed from *β*-ketocarboxylic acids, various primary amines, and 2-carboxybenzaldehyde via cetrimonium bromide salt-promoted multicomponent cascade of decarboxylation/lactamization reaction. This methodology features a simple, environmentally friendly approach, employing water as a green solvent and using a one-pot, three-component reaction. The synthesized compounds were evaluated for their antimicrobial activity in vitro against six microorganisms, namely *Escherichia coli*, *Serratia*, *Staphylococcus aureus, Bacillus subtilis*, *Aspergillus niger*, and *Fusarium oxysporum*. The results revealed that these derivatives have a significant antimicrobial activity. In addition, the drug-likeness of these derivatives has been evaluated.

Graphic abstract



Keywords Microwave-assisted synthesis · Green solvent · Cetrimonium bromide · Isoindolinone derivatives · Antimicrobial activity

Introduction

Isoindolinone skeleton is an important privileged class in exhibiting a broad range of potent therapeutic and pharmacological activities [1, 2]. The isoindolinone moiety is found in natural products and biologically active compounds [3, 4]. Examples of biological activities of isoindolinone derivatives include therapeutic agents such as pagoclone (**A**) and pazinaclone (**B**) which showed anxiolytic and hypnotics activities [5, 6]. Zopiclone (**C**) is found to be clinically useful in the treatment of sedative effects [7] and compound **D** exhibited an inhibitory potency toward aldose reductase [8]. Furthermore, compound **E** appears to be an important agent to evaluate the potential therapeutic of ELOVL6 and ELOVL3 inhibitors [9] (Fig. 1).

Several methodologies for the synthesis of isoindolinone derivatives have been reported in the literature, including Mukaiyama/Mannich lactamization [10], Ugi/Diels–Alder reaction [11], Sonogashira coupling, followed by ring closure and redox reactions [12] and cascade reactions [13, 14]. Reportedly, in some methods various catalysts have been explored in the synthesis of isoindolinone derivatives such as camphorsulfonic acid (±)-CSA [15], DBU [16], bis(triphenylphosphine)palladium(II) dichloride [17], rhodium(III) [18], L-proline [19], Ru(II) [20], and $In(OTf)_3$ [21]. Nevertheless, the reported methodologies generally

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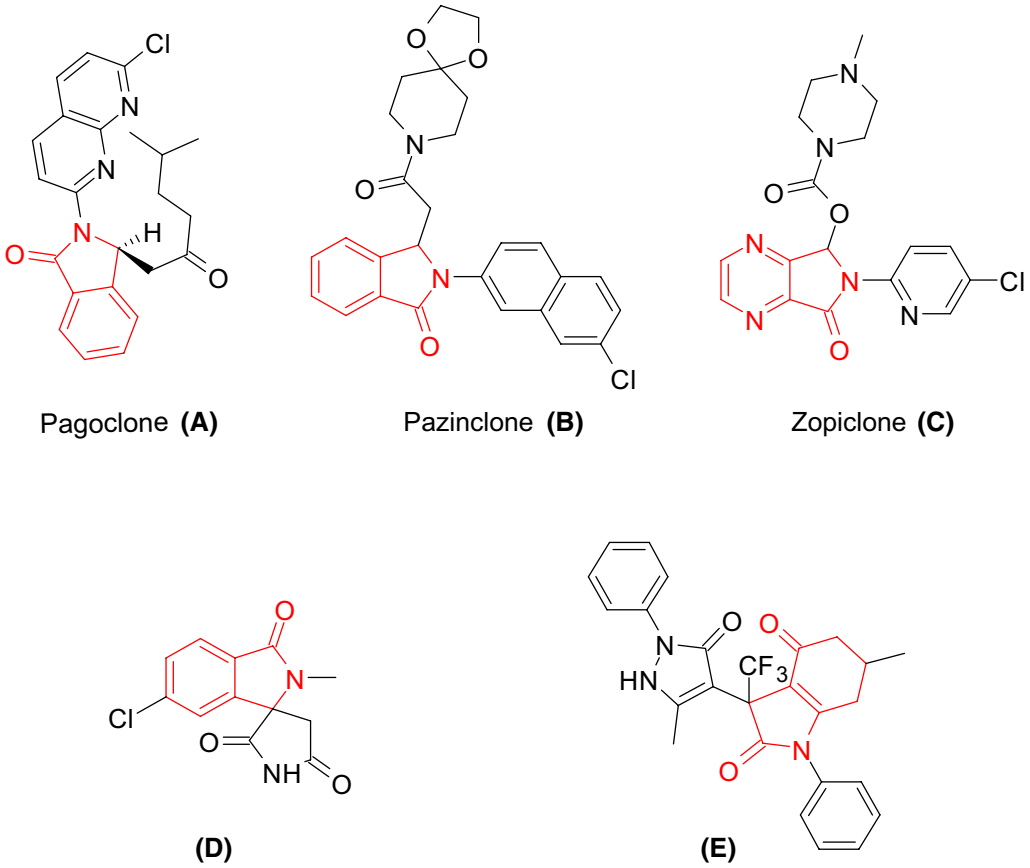


Fig. 1 Some pharmacologically active isoindolinone derivatives

involve several drawbacks such as use of expensive catalysts, many reagents, long reaction times, harsh reaction conditions, multi-step strategy, and using toxic organic solvents [12]. Thus, the development of efficient and green methodologies for the synthesis of isoindolinone derivatives is highly needed.

In this context, the scope of green chemistry has been receiving a huge attention in medicinal and organic chemistry [22]. One of the key principles of green chemistry is avoiding the toxic solvents in chemical reactions or replacing hazardous solvents with environmentally friendly solvents. Water is a non-toxic and non-flammable solvent compared with common organic solvents. The use of water as a green solvent in the synthesis of isoindolinones has been undertaken as a high level of chemical research [23].

Also, green chemistry has encouraged the use of green synthetic methods. One method to address this target includes using microwave (MW) irradiation technique [24]. The advantages of using MW irradiation comprise an environmentally eco-friendly approach [25], promotion of solvent-free reactions [26], increase in product yields, reduction of reaction times, enabling a concise control of the reaction conditions [27], and minimizing side-products [28]. MW irradiation has been extensively applied in the field of organic synthesis, especially in multicomponent reactions (MCRs) [29]. MCRs offer an important synthetic methodology over linear methodology due to their simplicity and unique ability to generate high structural complexity with minimum synthetic steps [30, 31]. In continuation of our work to adopt the advantages of MW irradiation and multicomponent reactions, we herein aim to use MW irradiation, cetrimonium bromide (cetyltrimethylammonium bromide, CTAB) as a cheap catalyst and water as a green solvent for the synthesis of novel isoindolinone derivatives **4a**–**4j** in a one-pot reaction. The isoindolinone derivatives **4a**–**4j** have been screened for their antimicrobial activity as a continuation of our research toward antimicrobial lead construction and the drug-likeness of these derivatives has been evaluated.

Results and discussion

Chemistry

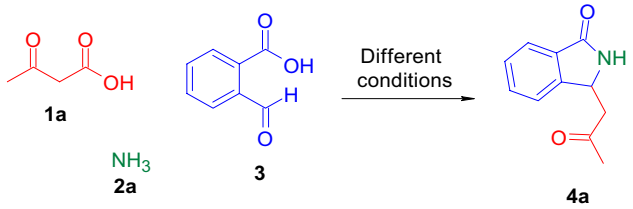
β-Ketocarboxylic acids are efficiently used to provide ketone enolate via decarboxylation process. The ketone enolate

reacts with many electrophilic partners and used in a variety of decarboxylative transformations. The model reaction was selected from the reaction of 3-oxobutanoic acid (**1a**, 2.5 mmol), ammonium hydroxide (**2a**, 32%, 6 mmol), and 2-carboxybenzaldehyde (**3**, 1 mmol) in order to synthesize isoindolinone derivative **4a**. The reaction did not proceed in the absence of catalyst as shown in Table 1 (entries 1 and 2). To our knowledge, the decarboxylation/lactamization reaction by using CTAB as a quaternary ammonium salt is unprecedented. The use of CTAB is found to be a significant catalyst for an activation of decarboxylation reaction in the presence of water as non-toxic solvent with only CO_2 generated as non-hazardous waste. To evaluate the efficiency of CTAB compared to the reported catalysts, the model reaction was tested in some of these catalysts including (±) CSA, L-proline, and DBU (Table 1, entries 3–7). Notably, an efficient activity of catalyst (CTAB) was noted and the desired product **4a** was obtained in higher yield in water. Thus, the effective concentration of CTAB was investigated for the model reaction in water as a solvent. Firstly, at the catalytic concentration of CTAB (20 mol%), the model reaction was carried out at 20 min and afforded the desired product **4a** 70% in yield (Table 1, entry 8). By increasing the reaction time from 20 min to 30 min, the highest yield of the desired product **4a** was obtained (Table 1, entry 9). Increasing the catalyst loading from 20 to 40 mol%, no a significant yield was obtained at the same reaction time (30 min) (Table 1, entry 10). As a result, 20 mol% of CTAB, water as a solvent, and reaction time 30 min were chosen as the most appropriate microwave conditions for the synthesis of novel isoindolinone derivatives **4a**–**4j** (Scheme 1).

The further extension of the present methodology was focused on using various primary amines such as tryptamine (**2b**), 2-phenylethanamine (**2c**), 4-(4-methoxyphenoxy)aniline (**2d**), 2-aminopyrimidine (**2e**), 4-(1*H*-imidazol-1-yl)-aniline (**2f**), 4-aminoquinaldine (**2g**), and 2-aminobenzothiazole (**2h**) under optimized conditions. We speculated that the multicomponent cascade of decarboxylation/lactamization reaction was delicately influenced by the electronic nature of the substituted amines. Notably, different yields of the corresponding isoindolinone derivatives varied with different amines. In the presence of ammonium hydroxide and aryl-alkylamines **2b**, **2c**, the reaction yields were considerably increased, affording the corresponding isoindolinones 75–85% yields. The result also revealed that aromatic amines with electron-donating substituents such as a methoxy group afforded high yields than non-substituent aromatic amines.

Our postulated mechanism for the formation of isoindolinone derivatives **4a**–**4j** has been tentatively proposed (Scheme 2). First of all, *β*-ketocarboxylic acid was

Table 1 The optimized conditions for the synthesis of isoindolinone derivative **4a**

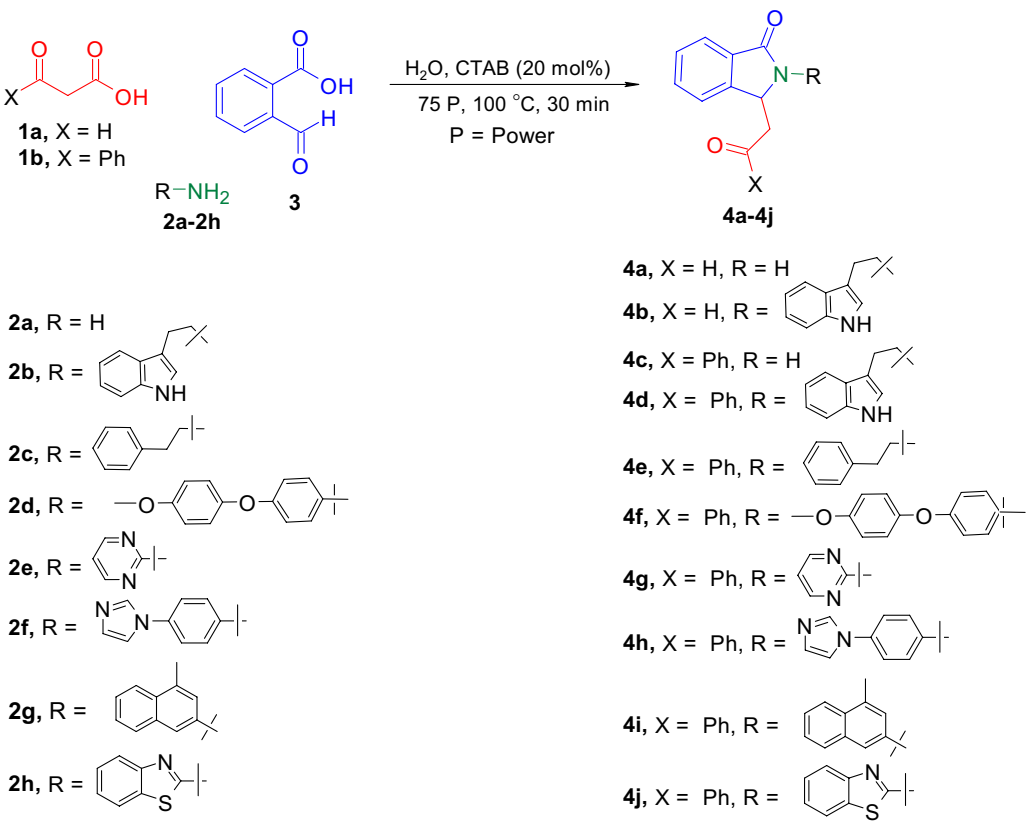


Entry	Method	Catalysis	Solvent	Temp/°C	Time	Yield/%[a]
1	Batch	None	MeOH	r.t.	24/h	–
2	Batch	None	MeOH	Reflux	10/h	–
3	Batch	(±)-CSA (20/mol%)	DMSO	Reflux	8/h	35
4	MW	(±)-CSA (20/mol%)	DMSO	100, 75 P	30/min	32
5	MW	L-proline (20/mol%)	MeOH	100, 75 P	30/min	35
6	MW	DBU (20/mol%)	DMSO	100, 75 P	30/min	42
7	MW	DBU (40/mol%)	DMSO	100, 75 P	30/min	50
8	MW	CTAB (20/mol%)	Water	100, 75 P	20/min	70
9	**MW**	**CTAB (20/mol%)**	**Water**	**100, 75 P**	**30/min**	**80**
10	MW	CTAB (40/mol%)	Water	100, 75 P	30/min	65

Bold values indicate the best microwave conditions for the synthesis of novel isoindolinone derivatives

[a]Isolated as a pure product

Scheme 1



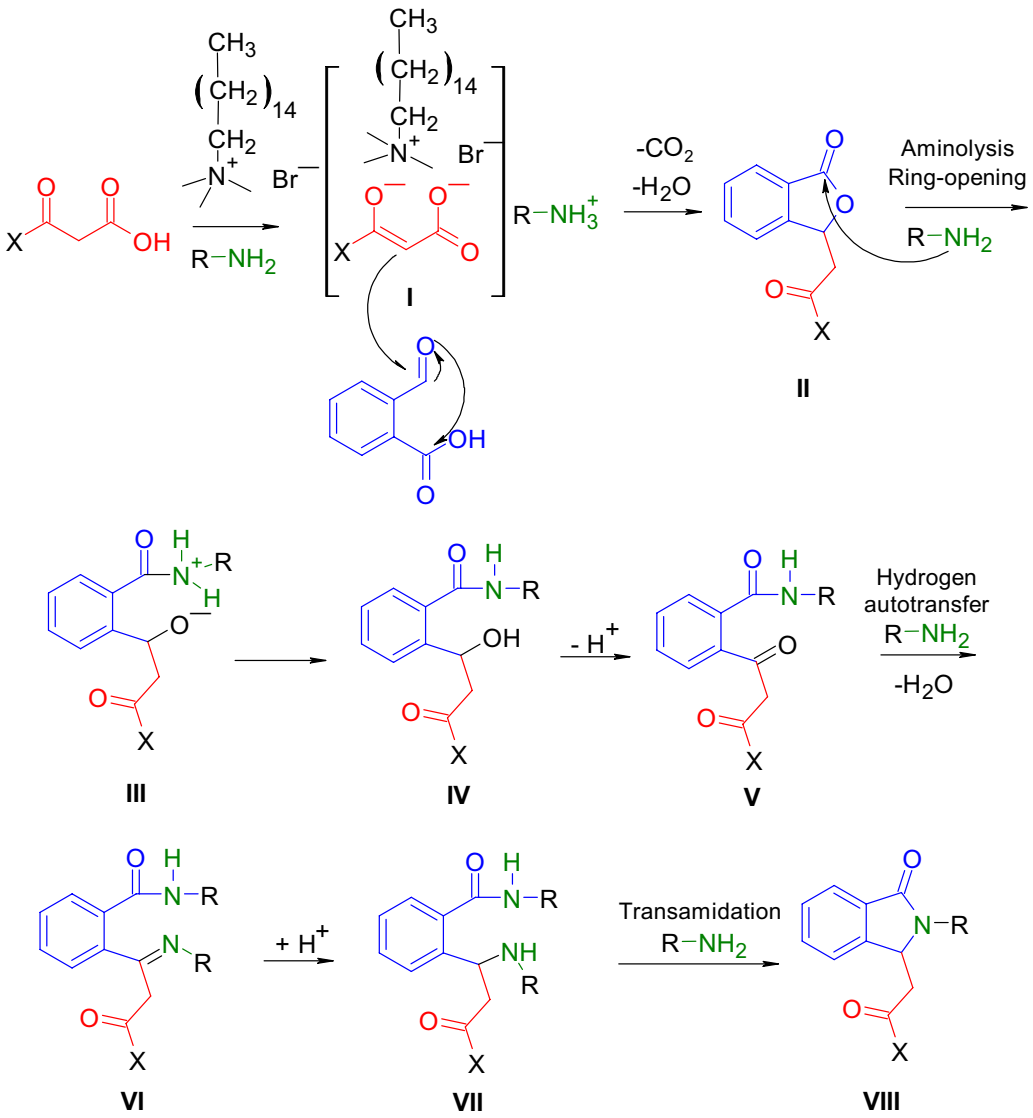
deprotonated by amine in the presence of ammonium salt (CTAB) to form dianion (an intermediate **I**) via the electrostatic interaction which forms between the lone pair of the substrate (two oxygen atoms) and the ammonium cation [32]. The further condensation between the intermediate **I** and 2-carboxybenzaldehyde gives an intermediate **II** (lactone) which subsequently undergoes a decarboxylative addition and further ring-closing reaction. On the basis of the proposed mechanism of lactone aminolysis (lactone ring-opening) in the literature [33], this mechanism involves three sequential chemical transformations. Initially, the carbonyl group of lactone **II** is aminolyzed by an extra addition of primary amine, forming the corresponding hydroxyamide **IV** via a zwitterionic intermediate **III**. The formation of the zwitterionic aminolysis intermediate **III** is rapid inference for the present lactone **II**. Then, an addition of proton to the hydroxyamide **IV** affords ketoamide **V**. After that, the N-alkylation of a primary amine with the ketoamide **V** via "hydrogen autotransfer" gives the corresponding aminoamide **VII**. Finally, the aminoamide **VII** undergoes intramolecular transamidation to afford the desired product **VIII**.

Biological activity

The bacterial microorganisms species used in this work included bacterial species: Gram-negative bacteria (*Escherichia coli* and *Serratia*) and Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*). These microorganisms were collected from the culture collection of microbiology constitute (Molecular Biology Lab, Government College University, Pakistan). Antibacterial activity of the synthesized compounds **4a**–**4j** was screened in an in vitro assay against these types of bacterial strains. The plates of assay were inoculated with the bacterial test via an addition of 1 cm^3 which contains diluted inoculums (106–107 CFU/cm^3) to the media after solidification. The wells of these plates were made from the tested compounds (0.1 mg) dissolved in 1 cm^3 DMSO and poured into the wells. The incubation of these plates was further carried out at 37 °C for 48 h, thereafter the inhibitory zones were evaluated by diameters [34]. For positive controls, norfloxacin and spiramycin (0.1 mg/cm^3) were used as standard antibacterial drugs, while DMSO was employed as a negative control.

On the other hand, antifungal activity of the synthesized compounds **4a**–**4j** was screened against two pathogenic fungi, namely *Aspergillus niger* and *Fusarium oxysporum* by

Scheme 2



the poison plate method. These species of fungi were incubated in potato dextrose agar medium (PDA) at 25 ± 1 °C for 5 days to obtain a new mycelium assay for antifungal test. These mycelia were cut approximately 0.5 cm from stock medium. The mycelia were then picked up by a needle of a sterilized inoculation and further inoculated in the plate of PDA. The final concentration of the synthesized compounds **4a**–**4j** was adjusted to 0.1 mg, dissolved in 1 cm^3 DMSO and added to the PDA (9 cm^3) in the culture medium. Fluconazole (0.1 mg/cm^3) was used as a standard antifungal drug for each experiment. All experiments were carried out in triplicate and the results were evaluated as zone of inhibition in mm.

Antibacterial activity

The antibacterial activity of the synthesized isoindolinone derivatives **4a**–**4j** was screened as mentioned in "Experimental" section. The results showed that most of isoindolinone derivatives **4a**–**4j** exhibited reasonable degrees of inhibition against the screened bacterial microorganisms. Table 2 shows that against *Escherichia coli*, *Serratia*, *Staphylococcus aureus*, and *Bacillus subtilis*, compounds **4a**–**4d** and **4h** showed the best results, in that the mean zones of inhibition were equal to 16–21 mm. Against the same microorganisms, compound **4g** showed moderate activity, with an inhibitory zone equal to 13–15 mm, followed by compounds **4j** and **4f** with mean zones of inhibition equal to 12–14 mm. The other synthesized compounds **4e** and **4i** exhibited inactivity against all strains of bacterial organisms.

Table 2 Antimicrobial activity expressed as zone of inhibition in diameter (mm) of novel isoindolinone derivatives **4a**–**4j**

Comp.	Antibacterial activity				Antifungal activity	
	E. coli	*Serratia*	*S. aureus*	*B. subtilis*	*A. niger*	*F. oxysporum*
4a	**19**	**20**	**18**	**17**	**19**	**20**
4b	**20**	**18**	**21**	**18**	**18**	**16**
4c	**16**	**19**	**19**	**16**	**18**	**16**
4d	**16**	**20**	**21**	**16**	**22**	**17**
4e	5	NA	NA	NA	NA	NA
4f	12	12	13	13	14	14
4g	14	13	15	13	**17**	14
4h	**18**	**20**	**18**	**18**	**21**	**18**
4i	NA	NA	NA	NA	NA	NA
4j	13	12	14	13	**16**	13
NFX	**20**	**25**	**22**	**20**	NT	NT
SPI	**19**	**23**	**21**	**22**	NT	NT
FCN	NT	NT	NT	NT	**24**	**22**

The bold font shows that compounds demonstrate a good activity

NT not tested, *NA* no activity, *NFX* norfloxacin, *SPI* spiramycin, *FCN* fluconazole. The blank of each experiment was performed with the same concentration of DMSO

Antifungal activity

The results obtained from the present test expressed a different behavior of isoindolinone derivatives **4a**–**4j** in the antifungal test (Table 2). The antifungal activity of the screened compounds showed that against *Aspergillus niger* and *Fusarium oxysporum*, compounds **4a**–**4d** and **4h** exhibited best results, with inhibitory zones equal to 16–22 mm. Against *Aspergillus niger*, compounds **4g** and **4j** showed good results, with mean zones of inhibition equal to 16–17 mm, while compound **4f** exhibited moderate activity against these types of fungal microorganisms. Against *Aspergillus niger* and *Fusarium oxysporum*, compounds **4e** and **4i** exhibited inactivity against these types of fungal microorganisms.

Drug-likeness

Drug-likeness is a considerable guideline for the beginning stages of drug discovery. Encouraged by the above result, this led to our focus on the adoption of drug-likeness protocol in order to investigate the substituent patterns of the screening compounds. These substituent patterns may positively affect a number of molecular properties. Thus, our research focused on an expedient synthesis of isoindolinone derivatives as a means to access medicinally relevant derivatives with their potential applications for extension of structural variation.

Given the initial supposition that isoindolinone derivatives of general structure **4a**–**4j** would have desirable properties from a standpoint of drug discovery, the isoindolinone derivatives **4a**–**4j** were evaluated using the quantitative estimate of drug-likeness (QED) parameter reported by Bickerton et al. [35]. The QED parameters were calculated using the implementation of the QED_w (weighted QED) algorithm which is available in the FAF-Drugs 4 online service [36]. The QED methodology describes eight molecular properties combined with drug-likeness and considers a score ranging from zero (all properties unfavorable) to one (all properties favorable). The score distribution was calculated for isoindolinone derivatives **4a**–**4j** (Fig. 2a), showing a reasonable degree of drug-likeness since the median scores of QED_w for these derivatives was 0.58. When the obtained data for all isoindolinone derivatives **4a**–**4j** are displayed as a cumulative frequency plot (Fig. 2b), it seems that some derivatives possess a QED_w score greater than 0.58, with a median value for the score distribution of 0.61. Favorably, compared to the score (median QED_w) of 0.63 introduced for a set of 771 oral drugs in Bickerton's original report [35]. The QED_w scores ranked structures were ordered as follows: compound **4d** (QED_w 0.621), compound **4b** (QED_w 0.610), compound **4h** (QED_w 0.584), compound **4f** (QED_w 0.581), compound **4j** (QED_w 0.563), compound **4g** (QED_w 0.556), compound **4i** (QED_w 0.528), and compound **4c** (QED_w 0.502).

When isoindolinone derivatives **4a**–**4j** were analyzed using the drug-like filter of FAF-Drugs 4, 9/10 compounds passed with the only exception being **4a** (isoindolinone structural alert). Moreover, 4/10 were expected to possess a good aqueous solubility, and 7/10 given log *P* values below 3. The value of log *P* distribution which calculated by the XLOGP3 strategy [37] is shown in Fig. 3c (median 2.02, IQR 1.50–2.55). The preceding results reflect the value of selecting to focus on the substituent patterns on amine, and the core-structure of these derivatives since

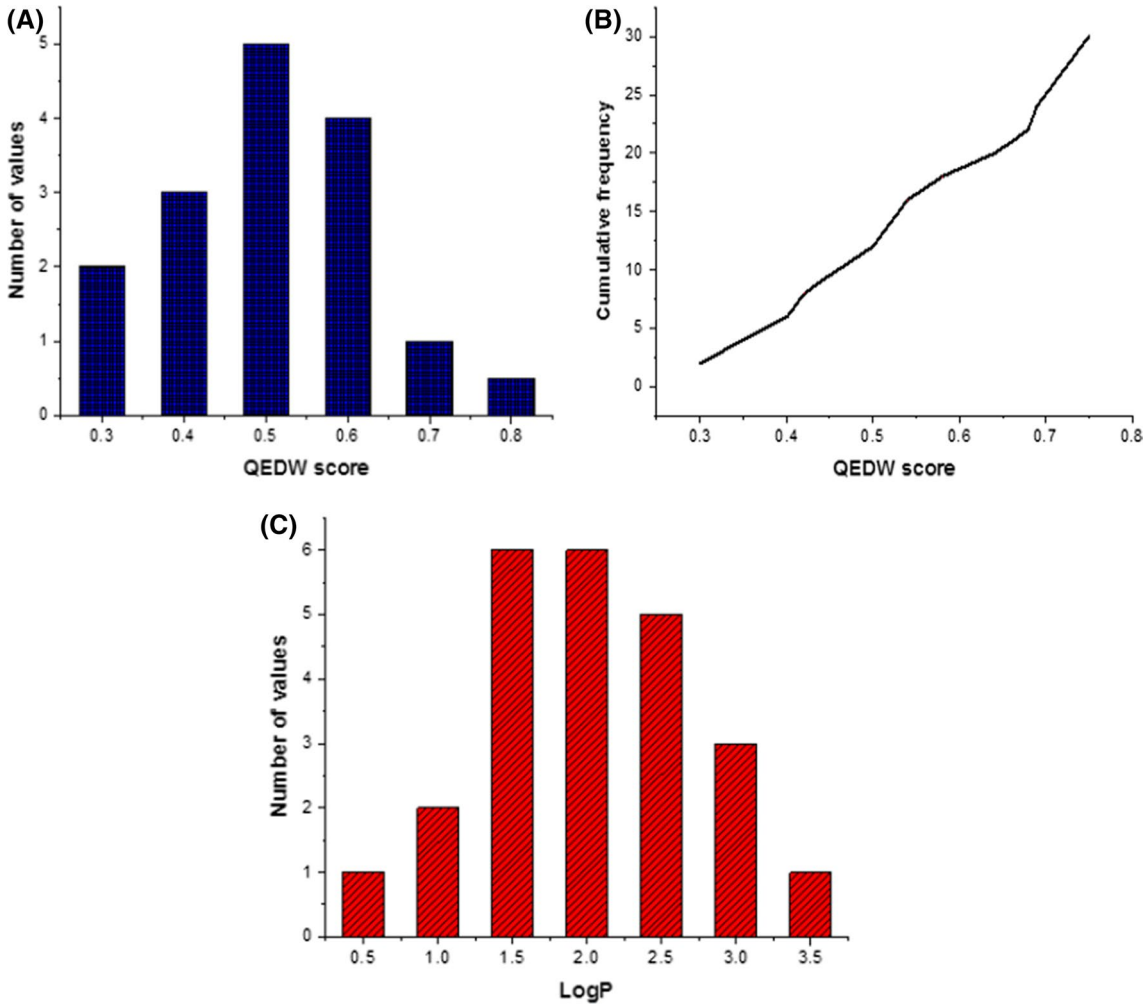


Fig. 2 The present isoindolinone derivatives **4a**–**4j** display favorable drug-like properties. **a** QED_w score distribution for isoindolinone derivatives **4a**–**4j**. **b** A cumulative distribution plot of QED_w scores for isoindolinone derivatives **4a**–**4j**. **c** Distribution of calculated log *P* values for isoindolinone derivatives **4a**–**4j**

the present protocol has shown that some derivatives are being predicated to have a good aqueous solubility and avoid presenting an excessive lipophilicity. Given their favourable drug-likeness, it is interesting to observe that some of these derivatives may have potential applications in medicinal chemistry.

Conclusion

In conclusion, we have proved a green, rapid, and highly efficient one-pot reaction under microwave strategy for the synthesis of novel isoindolinone derivatives through decarboxylation/lactamization cascade reaction in water. This strategy tolerates β-ketocarboxylic acids, various primary amines, 2-carboxybenzaldehyde, and cetrimonium bromide as a catalyst to afford a wide variety of isoindolinone derivatives in good yields. Cetrimonium bromide as quaternary ammonium salt plays an important role in this environmentally friendly decarboxylative lactamization/transformation. The obtained isoindolinone derivatives showed a good antimicrobial activity against six types of microorganisms, namely *Escherichia coli*, *Serratia*, *Staphylococcus aureus*, *Bacillus subtilis*, *Aspergillus niger*, and *Fusarium oxysporum*. Drug-likeness of these derivatives is evaluated by the quantitative estimate of drug-likeness (QED) method. The result showed that the most of these derivatives typically provide favorable drug-likeness properties. Such derivatives would therefore demonstrate to be a valuable extension to testing decks, and find their wide applications in drug discovery programs.

Experimental

Commercially available chemicals and solvents were ordered from Sigma Aldrich. All microwave reactions were carried out by using Smith Creator™ Optimiser EXP reactor (Vials™). Routine detecting of all reaction was performed by thin layer chromatography (TLC) with silica gel 60 UV 255 on plates pre-coated (Merck), and the spots were visualized with an alkaline aqueous solution of potassium permanganate ($KMnO_4$) or UV light. Flash column chromatography was performed by using silica gel 60 Å (230–400 mesh, Merck). Majority of the synthesized compounds was obtained in > 95% purity. Melting points were measured with Gallenkamp melting point apparatus in capillary tubes. Mass spectrometry was performed on a Micro Mass LCT operating in Electrospray mode (ES) (Leicester, UK). Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 100 FT-IR spectrophotometer (Perkin Elmer, Leicester, UK) using KBr pellets in the range 4000–500 cm^{-1}, and characteristic peaks are expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were run on Bruker AV-400 spectrometer at 400 MHz (^1H) and 100.5 MHz (^{13}C) at room temperature (Leicester, UK). Deuterated chloroform was used as the internal solvent (^1H NMR: $CDCl_3$: $\delta = 7.26$ ppm; ^{13}C NMR: $CDCl_3$: $\delta = 77.16$ ppm). Chemical shifts are expressed in parts per million (ppm) from tetramethylsilane (TMS) with the solvent resonance as the internal standard. The abbreviated pattern is used to express the multiplicities: s for singlet; d for doublet; dd for doublet of doublets, t for triplet and m, multiplet. The completed protons of decoupling *J* are evaluated by Hz unite. HPLC analysis for the synthesized compounds was performed by using Phenomenex lux cellulose-1 3 µm column (4.6 mm × 250 mm), 20% IPA in hexane, over 25 min, UV detection at 228 nm.

3-Oxobutanoic acid (**1a**) [38] and 3-oxo-3-phenylpropanoic acid (**1b**) [39] were prepared according to literature methods.

Microwave synthesis of isoindolinone derivatives

All microwave reactions were carried out in a capped (10 cm^3) microwave-vessel (borosilicate glass vial sealed) which was fitted in a microwave cavity. The pressure was set at 17 bar (average of an effective pressure = 4 bar) with power 75 W. A mixture of β-ketocarboxylic acid **1a** or **1b** (6.0 mmol), primary amine **2a**–**2h** (6.0 mmol), and CTAB (0.2 mmol, 20 mol%) in 3 cm^3 water was stirred for 5 min. To this mixture, 2-carboxybenzaldehyde (**3**, 1.0 mmol) was added and subjected to microwave irradiation at 100 °C for 30 min. When the reaction was completed (as indicated by TLC), the reaction vessel was cooled to room temperature and extracted with ethyl acetate (3 × 20 cm^3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was performed by a flash chromatography (eluent petroleum ether/ethyl acetate, 6:4) to afford the titled isoindolinone derivatives.

3-(2-Oxopropyl)isoindolin-1-one (4a) Compound **4a** was obtained as a pale solid. Yield 0.13 g (80%); *m.p.*: 130–131 °C. All the physical data were identical for those prepared previously (Ref. [40] *m.p.*: 131–133 °C).

2-[2-(1*H*-Indol-3-yl)ethyl]-3-(2-oxopropyl)isoindolin-1-one (4b, $C_{21}H_{20}N_2O_2$) Compound **4b** was obtained as an orange solid; yield 0.11 g (75%); *m.p.*: 101–102 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.04$ (s, 3H, CH_3), 2.55 (dd, 1H, $J = 8.5$, 2.1 Hz, CH), 2.84 (dd, 1H, $J = 7.6$, 3.1 Hz, CH), 3.17 (t, 2H, $J = 7.3$ Hz, CH_2), 3.48 (dd, 1H, $J = 13.9$, 6.8 Hz, CH), 4.27 (dd, 1H, $J = 7.3$, 2.8 Hz, CH), 5.0 (dd, 1H, $J = 4.1$, 2.1 Hz, CH), 7.67–7.07 (m, 6H, Ar–H), 7.71 (d, 1H, $J = 7.8$ Hz, Ar–H), 7.86 (d, 1H, $J = 6.6$ Hz, Ar–H), 8.06 (s, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.7$ (CH_3), 30.4 (CH_2), 41.1 (CH), 46.3 (CH_2), 55.5 (CH_2), 111.2 (Ar–CH), 112.9 (Ar–CH), 118.8 (Ar–CH), 119.6 (Ar–CH), 122.2 (Ar–CH), 122.5 (Ar–CH), 123.5 (Ar–CH), 127.3 (Ar–C), 128.4 (Ar–CH), 131.6 (Ar–CH), 132.0 (Ar–C), 136.3 (Ar–C), 145.6 (Ar–C), 168.3 (C=O), 205.8 (C=O) ppm; IR (KBr): $\bar{\nu} = 3468$ (N–H), 3056 (Ar–CH), 2986 (C–H), 1713 (C=O), 1681 (Ar–C=C) cm^{-1}; HRMS (ESI^+): *m/z* calcd for $C_{21}H_{20}N_2O_2$ ($[M+H]^+$) 333.1604, found 333.1598.

3-(2-Oxo-2-phenylethyl)isoindolin-1-one (4c) Compound **4c** was obtained as pale solid. Yield 0.11 g (75%); *m.p.*: 159–160 °C. All the physical data were identical for those prepared previously (Ref. [10] *m.p.*: 148–149 °C, Ref. [41] *m.p.*: 160–162 °C).

2-[2-(1*H*-Indol-3-yl)ethyl]-3-(2-oxo-2-phenylethyl)isoindolin-1-one (4d, $C_{26}H_{22}N_2O_2$) Compound **4d** was obtained as a red solid; yield 0.11 g (77%); *m.p.*: 108–109 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.05$–2.99 (m, 2H, CH_2), 3.21 (dd, 1H, $J = 12.1$, 3.6 Hz, CH), 3.36 (dd, 1H, $J = 12.8$, 5.0 Hz, CH), 3.57 (dd, 1H, $J = 16.1$, 6.5 Hz, CH), 4.22 (dd, 1H, $J = 16.3$, 7.0 Hz, CH), 5.31 (dd, 1H, $J = 7.4$, 4.9 Hz, CH), 7.51–7.4 (m, 7H, Ar–H), 7.60 (t, 1H, $J = 7.4$ Hz, Ar–H), 7.69 (d, 1H, $J = 7.8$ Hz, Ar–H), 7.90–7.78 (m, 4H, Ar–H), 8.10 (s, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.2$ (CH_2), 29.7 (CH_2), 41.9 (CH), 56.1 (CH_2), 118.6 (Ar–CH), 119.4 (CH, Ar), 119.5 (Ar–CH), 121.2 (Ar–CH), 122.1 (Ar–CH), 122.3 (Ar–C), 122.8 (Ar–C), 123.5 (Ar–C), 127.4 (Ar–CH), 128.1 (Ar–C), 128.4 (Ar–CH), 128.7 (Ar–C), 131.6 (Ar–CH), 132.1 (Ar–CH), 133.7 (Ar–C), 136.2 (Ar–C), 145.9 (Ar–C), 168.5 (C=O), 197.4 (C=O) ppm; IR (KBr): $\bar{\nu} = 3050$ (Ar–CH), 2915 (C–H), 1663 (C=O), 1616

(Ar–C=C) cm^{-1}; HRMS (ESI^+): *m/z* calcd for $C_{26}H_{22}N_2O_2$ ($[M+H]^+$) 395.1767, found 395.1754.

3-(2-Oxo-2-phenylethyl)-2-phenethylisoindolin-1-one (4e, $C_{24}H_{21}NO_2$) Compound **4e** was obtained as a yellow solid; yield 0.13 g (85%); *m.p.*: 145–146 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.09–2.98$ (m, 2H, CH_2), 3.16 (dd, 1H, $J = 17.8$, 6.9 Hz, CH), 3.29 (dd, 1H, $J = 17.6$, 6.8 Hz, CH), 3.45–3.36 (m, 2H, CH_2), 4.14 (dd, 1H, $J = 17.2$, 6.4 Hz, CH), 7.30–7.21 (m, 5H, Ar–H), 7.64–7.40 (m, 5H, Ar–H), 7.93–7.87 (m, 4H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.5$ (CH_2), 42.2 (CH_2), 42.9 (CH), 55.9 (CH_2), 122.7 (Ar–CH), 123.6 (Ar–CH), 126.5 (Ar–CH), 128.2 (Ar–CH), 128.4 (Ar–CH), 128.6 (Ar–CH), 128.8 (Ar–CH), 128.9 (Ar–CH), 131.7 (Ar–CH), 132.1 (Ar–C), 133.9 (Ar–CH), 136.3 (Ar–C), 138.9 (Ar–C), 145.8 (Ar–C), 168.5 (C=O), 197.3 (C=O) ppm; IR (KBr): $\bar{\nu} = 3057$ (Ar–CH), 2861 (C–H), 1681 (C=O), 1596 (Ar–C=C) cm^{-1}; HRMS (ESI^+): *m/z* calcd for $C_{24}H_{21}NO_2$ ($[M+H]^+$) 356.1651, found 356.1645.

2-[4-(4-Methoxyphenoxy)phenyl]-3-(2-oxo-2-phenylethyl)-isoindolin-1-one (4f, $C_{29}H_{23}NO_4$) Compound **4f** was obtained as a yellow solid; yield 0.12 g (72%); *m.p.*: 240–241 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.42$ (dd, 1H, $J = 17.9$, 7.3 Hz, CH), 3.80 (dd, 1H, $J = 18.7$, 8.9 Hz, CH), 3.85 (s, 3H, OCH_3), 6.20 (d, 1H, $J = 6.8$, 3.1 Hz, CH), 7.06–6.84 (m, 6H, Ar–H), 7.70–7.49 (m, 6H, Ar–H), 7.99–7.93 (m, 4H, Ar–H), 8.24 (d, 1H, $J = 9.3$ Hz, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 41.2$ (OCH_3), 43.7 (CH), 55.7 (CH_2), 115.1 (Ar–C), 120.9 (Ar–CH), 121.4 (Ar–C), 122.8 (Ar–CH), 123.9 (Ar–CH), 125.3 (Ar–CH), 125.9 (Ar–CH), 127.7 (Ar–CH), 128.8 (Ar–CH), 128.9 (Ar–CH), 129.5 (Ar–CH), 132.4 (Ar–C), 133.8 (Ar–CH), 133.9 (Ar–CH), 134.3 (Ar–C), 136.2 (Ar–C), 149.8 (Ar–C), 161.3 (Ar–C), 170.2 (C=O), 196.1 (C=O) ppm; IR (KBr): $\bar{\nu} = 3053$ (Ar–CH), 2836 (C–H), 1766 (C=O), 1684 (Ar–C=C) cm^{-1}; HRMS (ESI^+): *m/z* calcd for $C_{29}H_{23}NO_4$ ($[M+H]^+$) 450.1700, found 450.1698.

3-(2-Oxo-2-phenylethyl)-2-(pyrimidin-2-yl)isoindolin-1-one (4 g, $C_{20}H_{15}N_3O_2$) Compound **4g** was obtained as a pale solid; yield 0.1 g (65%); *m.p.*: 190–191 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.42$ (dd, 1H, $J = 17.6$, 7.4 Hz, CH), 3.81 (dd, 1H, $J = 17.6$, 6.7 Hz, CH), 6.21 (dd, 1H, $J = 6.8$, 2.9 Hz, CH), 7.70–7.49 (m, 9H, Ar–H), 8.00–7.94 (m, 3H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 43.7$ (CH), 55.9 (CH_2), 122.8 (Ar–CH), 123.4 (Ar–CH), 125.8 (Ar–C), 125.9 (Ar–C), 126.3 (Ar–C), 128.2 (Ar–C), 128.8 (Ar–CH), 129.2 (Ar–CH), 129.5 (Ar–C), 133.9 (Ar–C), 134.3 (Ar–CH), 136.9 (Ar–C), 149.8 (Ar–C), 170.2 (C=O), 196.6 (C=O) ppm; IR (KBr): $\bar{\nu} = 3059$ (Ar–CH), 2905 (C–H), 1766 (C=O), 1681 (Ar–C=C) cm^{-1}; HRMS (ESI^+): *m/z* calcd for $C_{20}H_{15}N_3O_2$ ($[M+H]^+$) 330.1252, found 330.1249.

2-[4-(1*H*-Imidazol-1-yl)phenyl]-3-(2-oxo-2-phenylethyl)isoindolin-1-one (4 h, $C_{25}H_{19}N_3O_2$) Compound **4h** was obtained as a colorless solid; yield 0.11 g (77%); *m.p.*: 150–151 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.42$ (dd, 1H, $J = 17.6$, 7.4 Hz, CH), 3.81 (dd, 1H, $J = 17.6$, 6.7 Hz, CH), 6.20 (dd, 1H, $J = 6.6$, 2.5 Hz, CH), 7.50 (s, 1H, $C_3N_2H_3$), 7.53–7.49 (m, 4H, Ar–H), 7.67 (d, 1H, $J = 2.2$ Hz, $C_3N_2H_3$), 7.70–7.60 (m, 5H, Ar–H), 7.83 (d, 1H, $J = 2.4$ Hz, $C_3N_2H_3$), 7.99–7.94 (m, 4H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.8$ (CH), 43.7 (CH_2), 122.9 (C, $C_3N_2H_3$), 124.8 (Ar–CH), 125.6 (Ar–C), 126.0 (Ar–CH), 126.2 (Ar–CH), 128.2 (Ar–CH), 128.4 (Ar–CH), 128.6 (Ar–CH), 128.8 (Ar–CH), 129.5 (Ar–CH), 130.7 (C, $C_3N_2H_3$), 133.1 (Ar–CH), 133.9 (Ar–C), 134.3 (Ar–CH), 136.1 (Ar–C), 136.8 (C, $C_3N_2H_3$), 137.1 (Ar–C), 149.8 (Ar–C), 170.2 (C=O), 196.1 (C=O) ppm; IR (KBr): $\bar{\nu} = 3062$ (Ar–CH), 2912 (C–H), 1766 (C=O), 1684 (Ar–C=C) cm^{-1}; HRMS (ESI^+): *m/z* calcd for $C_{25}H_{19}N_3O_2$ ($[M+H]^+$) 394.1556, found 394.1552.

2-(3-Methylnaphthalen-1-yl)-3-(2-oxo-2-phenylethyl)isoindolin-1-one (4i, $C_{26}H_{20}N_2O_2$) Compound **4i** was obtained as a yellow solid; yield 0.1 g (67%); *m.p.*: 160–162 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.58$ (s, 3H, CH_3), 3.41 (dd, 1H, $J = 15.3$, 4.9 Hz, CH), 3.81 (dd, 1H, $J = 15.6$, 5.8 Hz, CH), 6.21 (dd, 1H, $J = 6.6$, 3.1 Hz, CH), 7.37 (s, 1H, Ar–H), 7.38 (t, 1H, $J = 4.2$ Hz, Ar–H), 7.40 (s, 1H, Ar–H), 7.68–7.46 (m, 8H, Ar–H), 7.99–7.93 (m, 3H, Ar–H), 8.09 (d, 1H, $J = 8.3$ Hz, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.8$ (CH_3), 29.8 (CH), 43.7 (CH_2), 101.7 (Ar–C), 120.6 (Ar–CH), 121.3 (Ar–CH), 122.9 (Ar–C), 123.3 (Ar–CH), 124.8 (Ar–CH), 125.1 (Ar–C), 125.2 (Ar–CH), 125.8 (Ar–CH), 128.1 (Ar–CH), 128.2 (Ar–CH), 128.9 (Ar–CH), 129.4 (Ar–CH), 129.8 (Ar–CH), 130.1 (Ar–C), 130.6 (Ar–CH), 133.9 (Ar–C), 134.3 (Ar–C), 149.7 (Ar–C), 169.2 (C=O), 196.0 (C=O) ppm; IR (KBr): $\bar{\nu} = 3059$ (Ar–CH), 2925 (C–H), 1766 (C=O), 1666 (Ar–C=C) cm^{-1}; HRMS (ESI^+): *m/z* calcd for $C_{26}H_{20}N_2O_2$ ($[M+H]^+$) 393.1554, found 393.1560.

2-(Benzo[*d*]thiazol-2-yl)-3-(2-oxo-2-phenylethyl)isoindolin-1-one (4j, $C_{23}H_{16}N_2O_2S$) Compound **4j** was obtained as a yellow solid; yield 0.08 g (65%); *m.p.*: 142–143 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.81$ (dd, 1H, $J = 17.6$, 5.7 Hz, CH), 4.70 (dd, 1H, $J = 17.3$, 5.9 Hz, CH), 6.22 (dd, 1H, $J = 14.4$, 4.5 Hz, CH), 7.83–7.31 (m, 8H, Ar–H), 8.05–7.87 (m, 5H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.7$ (CH), 43.7 (CH_2), 121.3 (Ar–CH), 121.6 (Ar–CH), 122.8 (Ar–CH), 124.2 (Ar–CH), 124.5 (Ar–C), 124.6 (Ar–CH), 125.7 (Ar–CH), 125.9 (Ar–CH), 126.5 (Ar–CH), 128.2 (Ar–CH), 128.9 (Ar–C), 129.5 (Ar–CH), 130.6 (Ar–C), 131.2 (Ar–C), 133.9 (Ar–C), 136.2 (Ar–C), 149.8 (Ar–C), 168.9 (C=O), 196.1 (C=O) ppm; IR (KBr): $\bar{\nu} = 3057$ (Ar–CH), 2926 (C–H), 1766 (C=O), 1686 (Ar–C=C) cm^{-1}; HRMS

(ESI$^+$): *m/z* calcd for $C_{23}H_{16}N_2O_2S$ ($[M+H]^+$) 385.0960, found 385.0957.

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References

1. Palombi L, Di Mola A, Vignes C, Massa A (2014) Mol Divers 18:323
2. Sashidhara KV, Singh LR, Palnati GR, Avula SR, Kant R (2016) Synlett 27:2384
3. Wu X, Wang B, Zhou Y, Liu H (2017) Org Lett 19:1294
4. Dhanasekaran S, Bisai V, Unhale RA, Suneja A, Singh VK (2014) Org Lett 16:6068
5. Stuk TL, Assink BK, Bates RC, Erdman DT, Fedij V, Jennings SM, Lassig JA, Smith RJ, Smith TL (2003) Org Process Res Dev 7:851
6. Gai X, Grigg R, Khamnaen T, Rajviroongit S, Sridharan V, Zhang L, Collard S, Keep A (2003) Tetrahedron Lett 44:7441
7. Carlson JN, Haskew R, Wacker J, Maisonneuve IM, Glick SD, Jerussi TP (2001) Eur J Pharm 415:181
8. Wrobel J, Dietrich A, Woolson SA, Millen J, McCaleb M, Harrison MC, Hohman TC, Sredy J, Sullivan D (1992) J Med Chem 35:4613
9. Takahashi T, Nagase T, Sasaki T, Nagumo A, Shimamura K, Miyamoto Y, Kitazawa H, Kanesaka M, Yoshimoto R, Aragane K (2009) J Med Chem 52:3142
10. Dhanasekaran S, Kayet A, Suneja A, Bisai V, Singh VK (2015) Org Lett 17:2780
11. Huang X, Xu J (2009) J Org Chem 74:8859
12. Al-Jaroudi Z, Mohapatra PP, Jha A (2016) Tetrahedron Lett 57:772
13. Medimagh R, Marque S, Prim D, Marrot J, Chatti S (2009) Org Lett 11:1817
14. Petronzi C, Collarile S, Croce G, Filosa R, De Caprariis P, Peduto A, Palombi L, Intintoli V, Di Mola A, Massa A (2012) Eur J Org Chem 2012:5357
15. Srivastava A, Mobin SM, Samanta S (2104) Tetrahedron Lett 55:1863
16. Devineau A, Pousse G, Taillier C, Blanchet J, Rouden J, Dalla V (2010) Adv Synth Catal 352:2881
17. Kundu N, Wahab Khan M, Mahanty J (1999) J Chem Res Synopses 460
18. Zhu C, Falck JR (2012) Tetrahedron 68:9192
19. Bisai V, Unhale RA, Suneja A, Dhanasekaran S, Singh VK (2015) Org Lett 17:2102
20. Wu X, Wang B, Zhou S, Zhou Y, Liu H (2017) ACS Catal 7:2494
21. Chen T, Cai C (2017) New J Chem 41:2519
22. Jeon SJ, Li H, Walsh PJ (2005) J Am Chem Soc 127:16416
23. Shen S-C, Sun X-W, Lin G-Q (2013) Green Chem 15:896
24. Polshettiwar V, Varma RS (2008) Chem Soc Rev 37:1546
25. Jassem AM, Dhumad AM, Almashal FA, Alshawi JM (2020) Med Chem Res 29:1067
26. Jida M, Deprez-Poulain R, Malaquin S, Roussel P, Agbossou-Niedercorn F, Deprez B, Laconde G (2010) Green Chem 12:961
27. Jida M, Malaquin S, Deprez-Poulain R, Laconde G, Deprez B (2010) Tetrahedron Lett 51:5109
28. Hügel HM (2009) Molecules 14:4936
29. Jiang B, Shi F, Tu S-J (2010) Curr Org Chem 14:357
30. Jassem AM, Al-Ajely HM, Almashal FAK, Chen B (2019) Russ J Gen Chem 89:2562
31. Jassem AM, Almashal FAK, Mohammed MQ, Jabir HAS (2020) SN Appl Sci 2:359
32. Li J, Li YL, Jin N, Ma AL, Huang YN, Deng J (2015) Adv Synth Catal 357:2474
33. Kim K, Hong SH (2015) J Org Chem 80:4152
34. Sgouras D, Maragkoudakis P, Petraki K, Martinez-Gonzalez B, Eriotou E, Michopoulos S, Kalantzopoulos G, Tsakalidou E, Mentis A (2004) Appl Environ Microbiol 70:518
35. Bickerton GR, Paolini GV, Besnard J, Muresan S, Hopkins AL (2012) Nat Chem 4:90
36. Lagorce D, Bouslama L, Becot J, Miteva MA, Villoutreix BO (2017) Bioinformatics 33:3658
37. Cheng T, Zhao Y, Li X, Lin F, Xu Y, Zhang X, Li Y, Wang R, Lai L (2007) J Chem Inform Mod 47:2140
38. Molodtsov V, Fleming PR, Eyermann CJ, Ferguson AD, Foulk MA, McKinney DC, Masse CE, Buurman ET, Murakami KS (2015) J Med Chem 58:3156
39. Kabalka GW, Yang K, Wang Z (2001) Synth Commun 31:511
40. Rao IN, Prabhakaran E, Das SK, Iqbal J (2003) J Org Chem 68:4079
41. Han FZ, Su BB, Jia LN, Wang PW, Hu XP (2017) Adv Synth Catal 359:146