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Research paper

Natural α-methylenelactam analogues: Design, synthesis and evaluation of α-alkenyl-γ and δ-lactams as potential antifungal agents against *Colletotrichum orbiculare*

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ABSTRACT

In our continued efforts to improve the potential utility of the α-methylene-γ-lactone scaffold, 62 new and 59 known natural α-methylenelactam analogues including α-methylene-γ-lactams, α-arylidene-γ and δ-lactams, and 3-arylideneindolin-2-ones were synthesized as the bioisosteric analogues of the α-methylenelactone scaffold. The results of antifungal and cytotoxic activity indicated that among these derivatives compound (*E*)-1-(2, 6-dichlorobenzyl)-3-(2-fluorobenzylidene) pyrrolidin-2-one (**Py51**) possessed good selectivity with the highest antifungal activity against *Colletotrichum orbiculare* with IC_{50} = 10.4 μM but less cytotoxic activity with IC_{50} = 141.2 μM (against HepG2 cell line) and 161.2 μM (against human hepatic L02 cell line). Ultrastructural change studies performed by transmission electron microscope showed that **Py51** could cause important cell morphological changes in *C. orbiculare*, such as plasma membrane detached from cell wall, cell wall thickening, mitochondria disruption, a dramatic increase in vacuolation, and eventually a complete loss in the integrity of organelles. Significantly, mitochondria appeared one of the primary targets, as confirmed by their remarkably aberrant morphological changes. Analysis of structure–activity relationships revealed that incorporation of the aryl group into the α-*exo*-methylene and the *N*-benzyl substitution increased the activity. Meanwhile, the α-arylidene-γ-lactams have superiority in selectivity over the 3-arylideneindolin-2-ones. Based on the results, the *N*-benzyl substituted α-(2-fluorophenyl)-γ-lactam was identified as the most promising natural-based scaffold for further discovering and developing improved crop-protection agents.

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1. Introduction

Emerging infectious diseases caused by fungi are increasingly recognized as a worldwide persistent threat to human, animal and plant health [1–4]. As a consequence of the infection, these diseases have recently caused the biodiversity loss in some regions, resulting in the severe species decline and measurable ecosystem-level changes in both animals and plants, and, more importantly, are jeopardizing the global food security [2,3]. Moreover, these threats are exaggerated in the landscape by fungal adaption to new ecosystem, generated by trade and transportation, and by climate changes [2]. To ensure the global food security, since 1960s the agrochemical industry provided agriculture with a vast array of synthetic chemicals for crop protection, including fungicides. According to their fungicidal effects on specific stages in the life cycle of the fungus, commercial fungicides could be classified into protective, curative, eradicative, and antisporulation types (Fig. 1) [5]. Over past decades, due to repeated use of these different types of fungicides with identical or similar mode of action, there has been a rapid increase in fungicide resistance, which is tightly associated with the failure of fungal diseases control in crops [6]. Meanwhile, non-target and environmental hazard of fungicidal chemicals has stimulated great public concern [7–9]. In addition, more stringent registration for agrochemicals has been implemented [10]. On these grounds, there is a continuing need for the development of new, effective and safe agrochemicals as the alternatives for the

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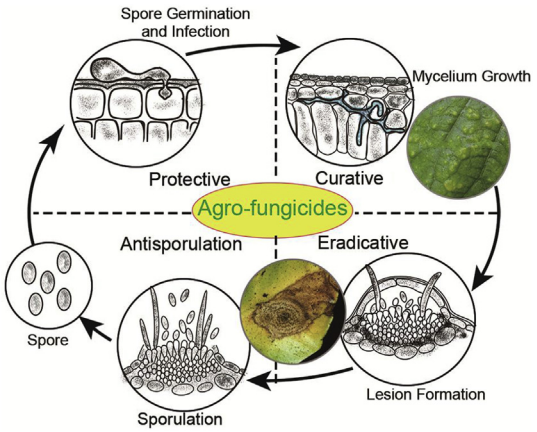


Fig. 1. Different types of commercial agro-fungicides were classified according to their fungicidal effects on specific stages in the life cycle of the fungus (*Colletotrichum* fungi presented in above figure).

fungal diseases control in crops.

Natural products are the masterpieces of nature's chemical laboratories and many of them or their analogues shared the features of bio- and environmental compatibilities, easy biodegradation, structural diversities and different mode of actions than existing pesticides [10–13]. That is the reason why natural product has long been used as pesticides and has broadly served as a source of inspiration for a great many commercial synthetic pesticides that are in the market today [10–18]. Therefore, the discovery of new antifungal compounds or scaffolds from natural products has been intensively focused recently as an important alternative for research and development of new fungicides.

In our original works, carabrone and its alcohol analogue carabrol (Fig. 2), two known sesquiterpene lactones isolated from the fruits of *Carpesium macrocephalum*, were found to possess potent antifungal activity against *Colletotrichum orbiculare* in a protective manner [19]. From the perspective of infection process of fungi and disease cycle, the protective antifungal agents, blocking early penetrative infection process of spores, play a superiorly preventive role in the subsequent disease development, and thus were liable to minimize the diseases control cost and crop losses. For this reason, the protective antifungal agents are very helpful in the crop disease control. Continuously, study of the structure-activity relationships of carabrone revealed that the bioactive scaffold α-*exo*-methylene-γ-lactone plays a crucial role in its activity profile [20,21]. Interestingly enough, the small, less functionalized analogues of naturally occurring α-methylene-γ-lactone are represented by tulipalin A and B (Fig. 2), which efficaciously replicate the effective antifungal ability of the complex natural products [22–24]. Noticeably, further exploitation of carabrone suffers from fussy total procedures. Accordingly, we concisely synthesized a collection of α-methylene-γ-lactone derivatives by virtue of pharmacophore strategy [25,26]. Though some of these derivatives are potent enough as the lead compounds for further optimization, there has some barriers hindering our effort to further research. Specifically,

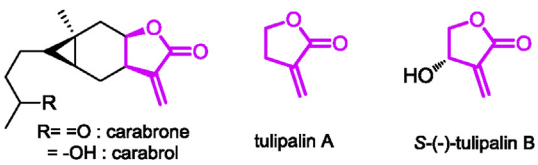


Fig. 2. Chemical structures of carabrone, carabol, tulipalin A and *S*-(−)-tulipalin B.

their cytotoxicity could not be negligible and they are not stable enough when applied in fields, which were plausibly attributed to the high electrophilicity of α-methylene-γ-lactone moiety, a Michael acceptors [27–29]. Thus this has prompted us to continue to seek new analogous template with improved efficacy and stability, and low toxicity.

α-Methylene-γ-lactam motif, a bioisostere of α-methylene-γ-lactone by the isosteric replacement of the oxygen with a nitrogen atom, occurs much less common in many natural products as well as the α-methylene-δ-lactam [30,31]. Examples of occurring compounds of this substructure include pukeleimid E [32], anatin and isoanatin [33] (Fig. 3). Natural or synthetic compounds containing this moiety show important biological activities, such as cytotoxic, antitumor and anti-inflammatory activities [30,31]. Nevertheless, it has been demonstrated that the α-methylene-γ-lactam scaffold in place of the γ-lactone moiety could help to mitigate their promiscuous biological toxicity [34]. Meanwhile, arylation of the α-methylene-γ-lactone substructure rendered α-benzylidene-γ-lactones, and a preliminary biological evaluation indicated that appropriate substituents on the α-benzylidene-γ-lactone functional group could reduce their toxicity [35,36]. On the other hand, the α-benzylidene-γ-lactam could be envisaged as the product of chain-ring transformation of cinnamamide derivatives, which received considerable attention as a result of their proven antifungal activity [37,38] (Fig. 3).

In this context, we firstly synthesized the α-methylene and benzylidene-γ-lactam by the isosteric replacement of the oxygen with a nitrogen atom, as it leads to a less reactive and hopefully more stable and selective system. Additionally, supplementary nitrogen atom allows for a variety of modulation by substituted with different lipophilic chain or aromatic rings for instance. To estimate the effect of ring conformation and constraints on the activity, a series of natural α-methylenelactam analogues α-benzylidene-δ-lactams and 3-benzylideneindolin-2-ones were synthesized and their antifungal activity was tested. Structure-activity relationships were investigated parallelly to provide a helpful insight into further lead optimization. The cytotoxicity and selectivity were sufficiently considered in the optimization. To investigate the ultrastructural changes of fungus induced by the potent analogue **Py51** and lay a preliminary foundation for the further antifungal mechanism studies on these compounds, transmission electron microscope (TEM) analyses were performed.

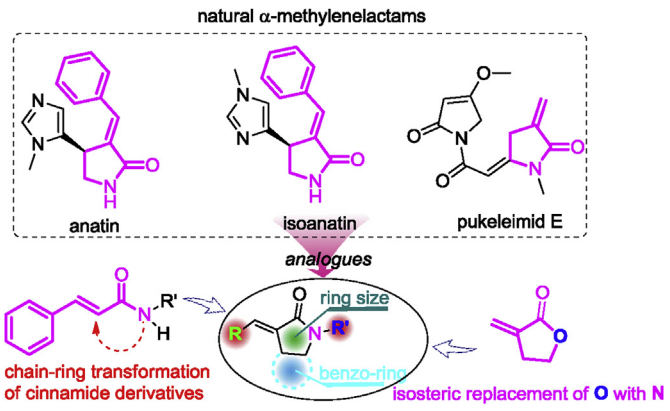


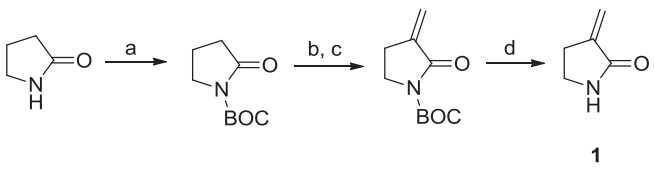
Fig. 3. Chemical structures of natural α-methylenelactams anatin, isoanatin, and pukeleimid E; and the design strategy for target molecules.

2. Results and discussion

2.1. Chemistry

Depending on the design strategy for the targeted scaffolds (Fig. 3), a variety of different compounds was prepared including α-methylene-γ-lactams, α-arylidene-γ and δ-lactams, and 3-arylideneindolin-2-ones, as outlined in Scheme 1-6. Previously, we reported that the natural α-methylene-γ-butyrolactone (tulipalin A) together with its analogues exhibited moderate to good inhibitory activity on the germination of spores of *C. orbiculare* [25,26]. On the basis of these results, we first investigated the influence of bioisosteric replacement of oxygen atom with NH on the inhibitory efficacy. Thus, α-methylene-γ-lactam was prepared using the known procedure (Scheme 1) [39,40]. A two-step sequence encompassing the protection of commercially available 2-pyrrolidone with di-*tert*-butyl dicarbonate (Boc_2O) and the reaction of *N*-Boc-2-pyrrolidone with diethyl oxalate in the presence of sodium hydride (NaH) provided an enolate intermediate. Subsequently, the enolate intermediate was reacted with paraformaldehyde, followed by elimination to give the desired 3-methylene functionality. Finally, removal of the *N*-Boc protection afforded α-methylene-γ-lactam **1**.

Next, we designed a patterned structural study of α-arylidene-γ and δ-lactams to obtain structure-activity information and to investigate the electrostatic, steric, hydrogen bonding requirements, and ring size for inhibitory activity. The preparation of these compounds by direct aldol type condensation of 2-pyrrolidone with aromatic aldehydes, however, seemed less efficient in comparison with its bioisostere, tulipalin A. Generally, there are two significant reasons for the impracticable implementation [41]. First, the α-hydrogens are much less acidic than those of γ-butyrolactone, which readily undergoes base-catalyzed aldol condensation with aromatic aldehydes. Second, there occur some crossed side reactions, including the Claisen condensation between the 2-pyrrolidones and addition of the lactam N-H moiety across the aldehyde carbonyl group. Nevertheless, it has been reported that a direct aldol condensation of 2-pyrrolidone with aromatic aldehydes could be accomplished if the lactam nitrogen function were protected with a sufficient electron withdrawing group, e.g. an acetyl or trifluoroacetyl group [41–43], which would enhance the acidity of the α-hydrogens and simultaneously protect the N-H moiety from reacting. Trifluoroacetyl is preferably selected for protection due to its strong electron withdrawing feature and easy detrifluoroacetylation in the presence of OH^- generated *in situ* under mild reaction conditions. Consequently, with the stereochemistry of the exocyclic double bond being exclusively *E* [41–43], this method is concise and stereospecific. With regard to the tolerance of substrates, it was found that *N*-trifluoroacetyl-2-pyrrolidone reacted smoothly with aromatic aldehydes possessing electron-releasing or withdrawing substituents in a base-catalyzed aldol-type condensation when the strong base potassium *tert*-butoxide (KO_tBu) was employed to give the α-arylidene-γ-lactams (Scheme 2). Particularly, the 3-chlorobenzaldehyde gave

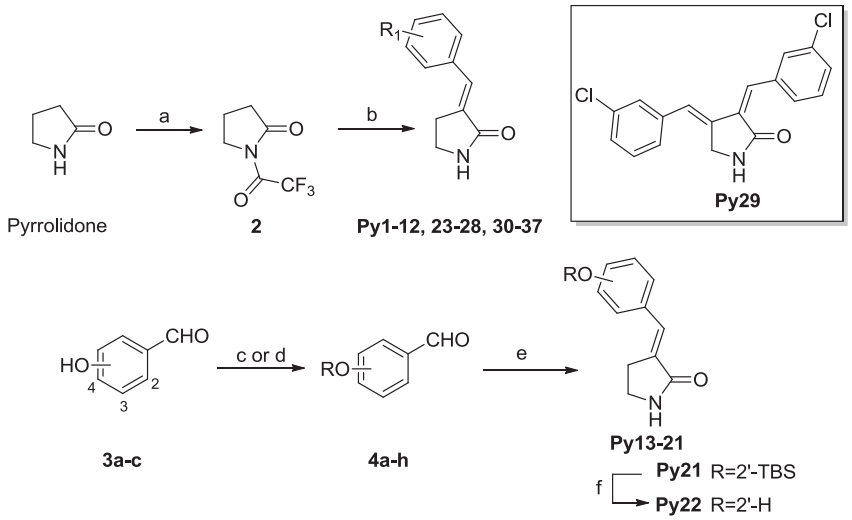


Scheme 1. Synthesis of α-methylene-γ-lactam. Reagents and conditions: a) Boc_2O, DMAP, Et_3N, DCM, r.t.; b) diethyl oxalate, NaH, Et_2O, 35°C; c) paraformaldehyde, DMF, 100°C; d) trifluoroacetic acid, DCM.

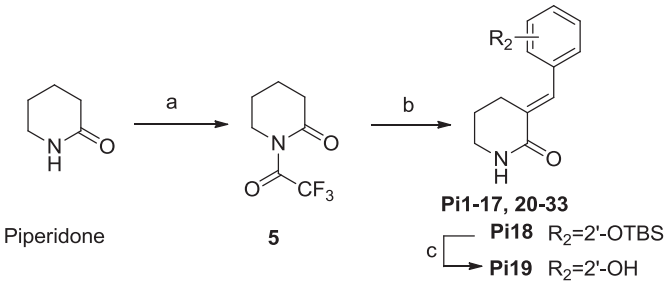
α, β-di(3-chlorobenzylidene)-γ-lactam which was identified by 2D NMR and mass spectrometry (Supporting Information), rather than the α-monosubstituted product. The hydroxyl compound **22** were synthesized through silyl protection of hydroxyl benzaldehyde using *tert*-butyldimethylsilyl chloride (TBSCl) and following deprotection of this ether group using tetrabutylammonium fluoride (TBAF) [44] (Scheme 2). The α-arylidene-δ-lactams were obtained in a similar way, while 3-chlorobenzaldehyde afforded the only α-monosubstituted product α-(3-chlorobenzylidene)-δ-lactam (Scheme 3).

Subsequently, to evaluate the essentiality of the benzo substituent on the β, γ-positions of γ-lactam ring, we synthesized a collection of 3-benzylideneindolin-2-ones **Ox1-28** with different substituents on the benzylidene ring by a Knoevenagel reaction [45]. The condensation reaction was carried out in ethanol with piperidine as base catalyst by reflux. Meanwhile, a set of analogues **Ox29–32** with different substituents on the indoline ring were synthesized to assess the impact of these substituents on efficacy of the efficiency 3-benzylideneindolin-2-one scaffold [46]. As shown in Scheme 4, the corresponding aniline was reacted with chloral hydrate ($Cl_3CCH(OH)_2$) and hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$) in aqueous sodium sulfate (Na_2SO_4) to form isonitrosoacetanilide followed by a Sandmeyer reaction with concentrated sulfuric acid to furnish the desired isatin in good yield. The reduction of corresponding isatin proceeded efficiently and conveniently with the low-valent Ti(0) reagent instead of the hydrazine hydrate involved in Wolff–Kishner reaction, giving to the oxidole analogues [47]. Finally, the 3-benzylideneindolin-2-ones with different substituents on the indoline ring were similarly synthesized by the Knoevenagel reaction. The 3-substituted indolin-2-ones may exist either the *Z* or *E* isomer depending on the characteristics of the substituents at C-3 position or at benzo ring of the 3-benzylideneindolin-2-one. To determine if these compounds were *E* or *Z* isomers, the chemical shifts of the aromatic protons on the benzylidene ring (H-2′ and H-6′) were analyzed. For the *Z* but not *E* isomer, the H-2′ or H-6′ protons would be shifted downfield due to deshielding by the carbonyl group. In the literature, chemical shifts of 7.45–7.84 ppm to the *E* isomer, and 7.85–8.53 ppm were assigned to the *Z* isomer [45,48,49]. For compounds already reported to be *E* isomers and whose chemical shifts were available from the literature, comparisons of our experimental values with reported values provided the stereochemical conformation. For compounds whose stereochemistries have not been previously assigned, the chemical shifts of the H-2′ and H-6′ protons in the molecules were used to conclude the configuration. The 2D NOE analysis was performed to determine the ratio of *Z* and *E* isomers. The *Z*-configured compounds showed a NOE effect between the protons at the C-4 position and vinyl proton of the 3-benzylideneindolin-2-ones [45,48,49]. The ratio of *Z*/*E* was determined by the integrals between the identified vinyl protons of *Z* and *E* isomers. The configuration and ratio of *Z*/*E* of these compounds were summarized in Table 4.

Furthermore, to check the involvement of the substituents on the lactam nitrogen atom in the potency and selectivity, we synthesized a group of N-substituted α-methylene-γ-lactams. The choice of substituents was guided by the Craig plot to ensure that groups of different lipohilicities and electronic effects were adequately represented. Starting from the optimized compound **Py25**, alkylation by halide using sodium hydride as a base in DMF solution afforded smoothly the corresponding alkylated products in quantitative yield [50] (Scheme 5). Ultimately, we synthesized N-substituted analogues **La1-3** with mere exocyclic methylene without substitution in an attempt to assess the significance of the benzylidene substituents. These N-substituted analogues, however, were not readily obtained by direct alkylation of α-methylene-γ-



Scheme 2. Synthesis of α-arylidene-γ-lactams. Reagents and conditions: a) TFAA, 0°C to r.t.; b) substituted benzaldehyde, KO_tBu, THF, 0°C–55°C; c) alkyl/benzyl bromide, K_2CO_3, DMF, 70°C; d) TBSCl, DMAP, Et_3N, THF, °C to r.t.; e) **2**, KO_tBu, 0°C–55°C, THF; f) TBAF, THF, r.t..



Scheme 3. Synthesis of α-arylidene-δ-lactams. Reagents and conditions: a) TFAA, 0°C to r.t.; b) substituted benzaldehyde, KO_tBu, THF, 0°C–55°C; c) TBAF, THF, r.t..

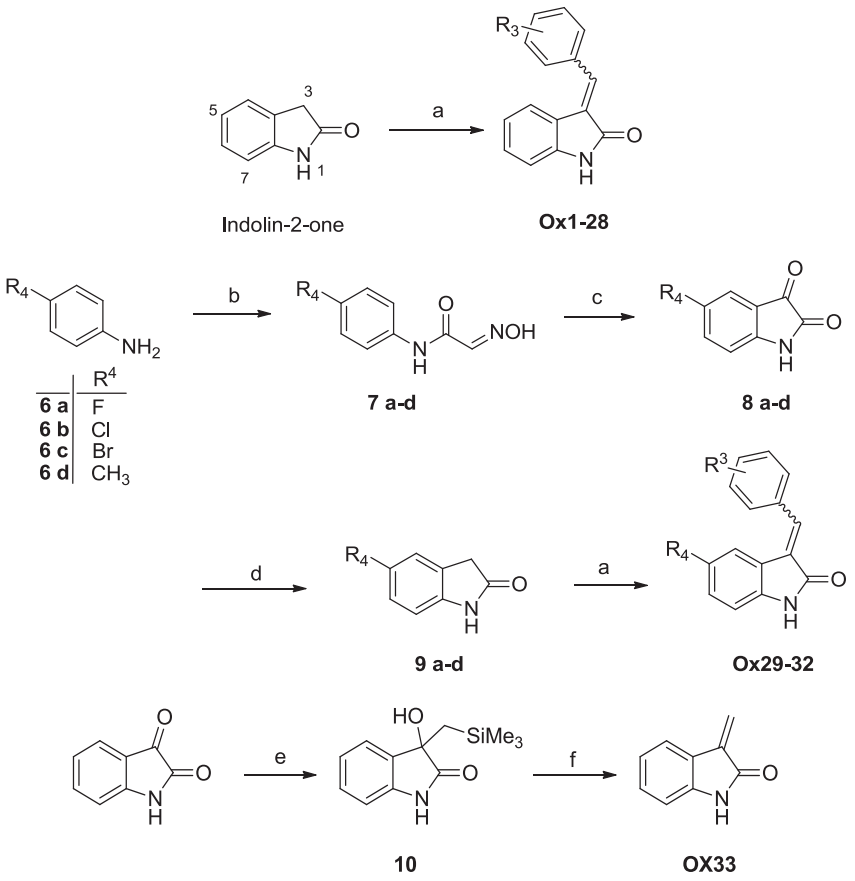
lactam due to the observable absence of stability in the strong base solution. Alternatively, we first prepared the Horner–Wadsworth–Emmons intermediates **12** by alkylation of 2-pyrrolidone followed by treatment of **11** with lithium diisopropylamide (LDA) and subsequent addition of diethyl chlorophosphate [51]. Then olefination of the formaldehyde using the lactams **12** as Horner–Wadsworth–Emmons reagents in the presence of sodium hydride furnished the targeted N-substituted α-methylene-γ-lactams **La1-3** in desirable yield [52] (Scheme 6). For the 3-methyleneindolin-2-one, the synthesis route utilized the versatile Peterson olefination of ketones via a β-silyl alcohol intermediate which could be obtained from the reaction of indolin-2-one with trimethylsilylmethylmagnesium chloride (Me_3SiCH_2MgCl) [53] (Scheme 4).

Altogether, 121 final products were synthesized, analyzed and tested, of which 62 are new compounds not previously described in the literature. Pure compounds (≥95% purity) were mostly obtained. The structure of the synthesized compounds were confirmed by ^1H and ^{13}C NMR spectroscopy, in addition to HPLC analysis coupled to electrospray ionization mass spectrometry (LC/ESI-MS) which was also used to determine the purity.

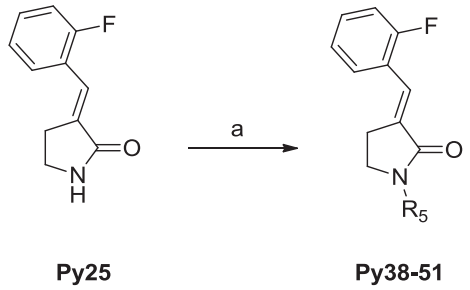
2.2. Antifungal activity and structure-activity relationship study

The α-methylene-γ-lactam (**1**) and (*E*)-3-benzylidenepyrrolidin-2-one (**Py1**) were chosen in the preliminary screening to identify the efficacy of the bioisosteric replacement and chain-ring transformation. A selection of economically important plant pathogenic fungi *Fusarium graminearum* Schw., *C. orbiculare*, *Botrytis cinerea*, *Fusarium oxysporum*, and *C. gloeosporioides* Penz. were screened. The results were summarized in Table 1. As shown, tulipalin A and compound **1** were active against nearly five fungi to various extents at 50 μg mL^{-1}. For the *C. orbiculare*, the lactam was slightly more potent than tulipalin A with inhibition ratios of 45.7% and 34.3%, respectively. Particularly, a similar trend in inhibitory activity was observed for these two analogues, which could be attributed to the bioisosteric effect that the bioisosteres may elicit a similar biological effect. In contrast, the transformational compound **Py1** displayed a superior activity to its acyclic analogue *N*-propylcinnamamide, which could be plausibly ascribed to the intrinsic biological feature of α-methylene-γ-lactams and deleterious flexibility of chain conformation of the cinnamamide derivatives. Therefore, these results validated our initial design strategy. Considering the high efficiency in activities of these two lactam prototype compounds **1** and **Py1** on *C. orbiculare* among the five tested fungi, the following screening was mainly focused on the *C. orbiculare*.

With the identification of efficacy of the bioisosteric replacement and chain-ring transformation, we continuously explored the optimal phenyl ring substitution of **Py1** for the antifungal activity against *C. orbiculare*. The antifungal activities were expressed as IC_{50} (50% inhibition concentration) and the results were shown in Table 2. Initial attempts to introduce electron-donating CH_3 at the *para*-, *meta*-, and *ortho*-position of the phenyl group of **Py1**, led to the conclusion that the *para*-CH_3 substitution is better, as it can be seen that compound **Py2** showed an improved IC_{50} of 44.7 μM. Meanwhile, the bulky group with branching chains at *para*-position conferred a dramatic potency decrease, while the CH_3CH_2 group restored modest antifungal activity compared with unsubstituted **Py1**. These results showed it essential for potency to possess a smaller alkyl group other than a branched group with larger volume and shape, which may interfere with receptor binding. The following introduction of electron-donation CH_3O group on the *para*-position led to a ~2-fold increase in activity for compound **Py8**. When the CH_3O was shifted from the *para*-position to the *ortho*- or *meta*-position, it triggered the identification of a potent *ortho*-OCH_3 compound **Py10** with IC_{50} of 77.5 μM but an impotent compound **Py9**. With the identification of analogues **Py8** and **Py10**, further SAR exploration was extensively carried out by replacing

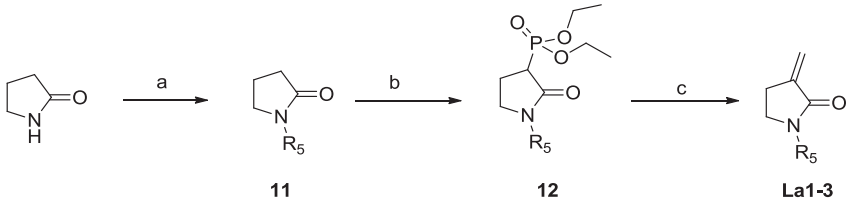


Scheme 4. Synthesis of 3-arylideneindolin-2-ones. Reagents and conditions: a) substituted benzaldehyde, piperidine (cat.), EtOH, reflux; b) $Cl_3CCH(OH)_2$, $NH_2OH \cdot HCl$, Na_2SO_4, H_2O, HCl, 55°C, overnight; c) H_2SO_4, 55–80 °C; d) $TiCl_4$/Zn, THF, r.t.; e) Me_3SiCH_2MgCl, Et_2O, −78°C to r.t.; f) $BF_3 \cdot OEt_2$, CH_2Cl_2, -78°C.



Scheme 5. Synthesis of N-substituted **Py25**. Reagents and conditions: a) alkyl/benzyl bromide, NaH, DMF, 0°C to r.t..

the CH_3O group with more bulky CH_3CH_2O, $CH_3(CH_2)_3O$, $(CH_3)_2CH(CH_2)_2O$, $CH_3(CH_2)_{11}O$, $C_6H_5CH_2O$ groups. Up to a four-carbon *O*-alkyl chain the activity level was retained. Particularly, the benzyl analogue **Py20** manifested a ~2-fold improved activity over Py**10**. Further increasing the chain length to five and twelve resulted in drastic loss of activity. Due to the *ortho*-alkoxyl substitution compounds exhibited higher potency than their *para*-analogues, the *ortho*-hydroxyl analogue **Py22** was prepared and its antifungal activity was evaluated. Somewhat unexpectedly, a considerable drop in potency was observed, despite the small size of the hydroxyl group and its ability to form hydrogen bonding. This is probably due to the decrease in cell penetration. Further SAR studies of electron-withdrawing groups on the phenyl ring were performed. Substitution at the *ortho*-position was strongly favored over the corresponding *meta*- and/or *para*-position as was confirmed in the high potent compounds **Py25** and **Py30**. While substitution of halogen atoms F, Cl and Br at other positions retained modest activity, lipophilic group $-CF_3$ was much less active. Of particular interest is the result obtained with **Py29**, which showed ~5-fold improved activity compared to the **Py1**. Additionally, we explored whether incorporating simultaneously two



Scheme 6. Synthesis of N-substituted α-methylene-γ-lactam. Reagents and conditions: a) alkyl/benzyl bromide, NaH, THF, 0°C to r.t.; b) LDA, diethyl chlorophosphate, THF, −5°C to r.t.; c) paraformaldehyde, NaH, THF, 0°C to r.t..

Table 1
Antifungal activities of tulipalin A, compound **1**, *N*-propylcinnamamide, and **Py1** at 50 μg mL^{-1}.

Compd	Inhibition of spore germination (%)[a]				
	F. graminearum Schw.	*C. orbiculare*	*B. cinerea*	*F. oxysporum*	*C. gloeosporioides* Penz.
tulipalin A	21.5	34.3	20.3	18.8	41.3
1	24.3	45.7	14.8	22.8	44.3
N-propylcinnamamide	30.0	28.0	34.5	52.0	38.5
Py1	52.5	63.0	33.8	44.0	31.3

[a] All the data was the average of three replications.

Table 2
The 50% inhibition concentration (IC_{50}) of compounds **Py1**–**37** against spore germination of *C. lagenarium*.

Compd	R_1	IC_{50}[a] (μM)	Compd	R_1	IC_{50} (μM)
Py1	H	176.9 ± 14.5	**Py20**	2-$C_6H_5CH_2O$	41.4 ± 1.3
Py2	4-CH_3	44.7 ± 8.4	**Py22**	2-OH	>250
Py3	3-CH_3	124.0 ± 9.2	**Py23**	4-$(CH_3)_2N$	>250
Py4	2-CH_3	>250	**Py24**	4-F	104.8 ± 6.5
Py5	4-CH_3CH_2	95.1 ± 5.9	**Py25**	2-F	38.9 ± 1.5
Py6	4-$(CH_3)_2CH$	>250	**Py26**	4-CF_3	>250
Py7	4-$(CH_3)_3C$	>250	**Py27**	2-CF_3	129.5 ± 11.7
Py8	4-CH_3O	92.9 ± 8.1	**Py28**	4-Cl	150.7 ± 14.0
Py9	3-CH_3O	176.8 ± 14.8	**Py29**	–	35.8 ± 2.3
Py10	2-CH_3O	77.5 ± 7.4	**Py30**	2-Cl	79.5 ± 6.4
Py11	4-CH_3CH_2O	184.3 ± 17.8	**Py31**	4-Br	>250
Py12	2-CH_3CH_2O	>250	**Py32**	3-Br	107.4 ± 9.4
Py13	4-$CH_3(CH_2)_3O$	>250	**Py33**	2-Br	94.9 ± 7.8
Py14	2-$CH_3(CH_2)_3O$	>250	**Py34**	2,3-diCl	112.3 ± 10.4
Py15	4-$(CH_3)_2CH(CH_2)_2O$	>250	**Py35**	3,4-diCl	>250
Py16	2-$(CH_3)_2CH(CH_2)_2O$	>250	**Py36**[b]	–	>250
Py17	4-$CH_3(CH_2)_{11}O$	>250	**Py37**[b]	–	>250
Py18	2-$CH_3(CH_2)_{11}O$	>250	Carbendazim	–	8.59 ± 1.9
Py19	4-$C_6H_5CH_2O$	60.1 ± 5.5			

[a] Note: All 50% inhibition concentration (IC_{50}) values are presented as the means ± SD (n = 4), μM.
[b] For compds **Py36** and **37**, the substituents on α-position of lactam ring are 9'-anthryl and 2'-naphthyl, respectively.

favorable substituents would provide synergistic effect. We observed that the disubstituted compounds **Py34** and **Py35** were less potent than the related monosubstituted analogue **Py30**. Finally, two bulky aryl groups, i.e., 9'-anthryl (**Py36**) and 2'-naphthyl (**Py37**), were introduced into the *exo*-methylene of lactam ring in replacement of the phenyl group. The obtained compound **Py36** and **Py37** possessed a loss in activity (IC_{50} > 250 μM). Overall, these results not only demonstrated that the *ortho*-position of the phenyl ring of **Py1** could tolerate both electron-donating and withdrawing groups much better than the *para*- or *meta*-position, but also confirmed the importance of substituents on the *ortho*-position with proper size or the electron-withdrawing characteristic.

Progressively, SAR studies to probe the core size of lactam ring were pursued by preparing a series of α-alkenyl-δ-lactams. As can be seen from Table 3, most of the analogues showed a significant loss of potency (IC_{50} > 250 μM). Although possessing the highest antifungal activity in this series of compounds, **Pi17** exhibited a remarkable drop in potency in contrast to its γ-lactam analogue **Py20**. Taken together, it could be supposed that the γ-lactam ring allows molecules to adopt conformations that more closely complement the topography of receptor binding sites, while the δ-lactam ring leads to a disruption of the bioactive conformation.

Our attention then turned to investigate the influence of the γ-lactam ring conformation on the potency. Taking advantage of the natural oxindole scaffold occurring a fully planar orientation of γ-lactam ring, a collection of 3-benzylideneindolin-2-ones with different substituents on the benzylidene ring were synthesized. Among these compounds, many of them were generally more potent than their corresponding γ-lactam analogues (see Table 4). It is tempting to attribute this profile to the increase in size, lipophilicity and rigidity of these compounds compared with the γ-lactam analogues due to the introduction of the benzo group. Nevertheless, these compounds with different substituents on the benzylidene ring still beared marked differences in antifungal activity where a number of interesting SAR trends could be obtained. A moderate deterioration of activity was observed for the electron-donating substituents CH_3, CH_3O, and CH_3CH_2O when they were installed into the *ortho*-, *meta*-, or *para*-position of the phenyl ring. Among these positions, activity varied to a small extent, suggesting that the three groups are not indispensable for the activity. Moreover, the bulky substituents isopropyl and *tert*-butyl were unfavorable to the activity. In the case of **Ox25**–**28**, the hydroxyl substitution resulted in a significant loss of inhibitory activity, suggesting that the hydroxyl group is disfavored. In contrast, the electron-withdrawing groups were instrumental in improving the potency. Particularly, **Ox18** with an electron-withdrawing group Cl proved to be the most potent compound. Accordingly, this SAR trend indicated a preference for electron-withdrawing group on the benzylidene ring of 3-benzylideneindolin-2-ones. By contrast to such a preference, disubstitution of the benzylidene ring with two halogens did not improve activity, as seen from a comparison of **Ox23**–**24** and **Ox17**–**19**. With *meta*-Cl group consistent on benzylidene ring, the indoline ring was decorated with different substituents including F (**Ox29**), Cl (**Ox30**), Br (**Ox31**), CH_3 (**Ox32**) to assess the impact of different substitutions on efficacy of the efficiency 3-benzylideneindolin-2-one scaffold. No obvious increase in activity was observed for compounds **Ox29** and **Ox32** but a clear decrease for **Ox30** and **Ox31**. A plausible explanation on such decreases is that the *Z* isomers existed and accounted for a considerable proportion in the *Z*/*E* mixtures (*Z*%, 65 in **Ox30**, 73 in **Ox31**). Ultimately, 3-methyleneindolin-2-one showed an improved activity than α-methylene-γ-lactam (**1**) and 3-benzylideneindolin-2-

Table 3
The 50% inhibition concentration (IC_{50}) of compounds **Pi1**–**32** against spore germination of *C. lagenarium*.

Compd	R_2	IC_{50}[a] (μM)	Compd	R_2	IC_{50}[a] (μM)
Pi1	H	>250	**Pi17**	2-$C_6H_5CH_2O$	105.2 ± 9.2
Pi2	4-CH_3	162.7 ± 13.9	**Pi19**	2-OH	>250
Pi3	3- CH_3	>250	**Pi20**	4-F	183.1 ± 16.0
Pi4	2-CH_3	>250	**Pi21**	2-F	>250
Pi5	4-CH_3CH_2	>250	**Pi22**	4-CF_3	>250
Pi6	4-$(CH_3)_2CH$	>250	**Pi23**	2-CF_3	124.0 ± 12.2
Pi7	4-$(CH_3)_3C$	>250	**Pi24**	4-Cl	>250
Pi8	4-CH_3O	152.3 ± 15.0	**Pi25**	3-Cl	>250
Pi9	3-CH_3O	>250	**Pi26**	2-Cl	>250
Pi10	2-CH_3O	>250	**Pi27**	4-Br	>250
Pi11	4-CH_3CH_2O	>250	**Pi28**	3-Br	>250
Pi12	2-CH_3CH_2O	>250	**Pi29**	2-Br	>250
Pi13	4-$CH_3(CH_2)_3O$	>250	**Pi30**	2,4-diCl	199.6 ± 18.1
Pi14	2-$CH_3(CH_2)_3O$	>250	**Pi31**	2,3-diCl	>250
Pi15	2-$(CH_3)_2CH(CH_2)_2O$	>250	**Pi32**	3,4-diCl	>250
Pi16	2-$CH_3(CH_2)_{11}O$	>250			

[a] Note: All 50% inhibition concentration (IC_{50}) values are presented as the means ± SD (n = 4), μM.

Table 4
The 50% inhibition concentration (IC_{50}) of compounds **Ox1**–**32** against spore germination of *C. lagenarium* and their *Z*/*E* isomer ratios.

Compd	R_3	R_4	% Z isomer	IC_{50}[a] (μM)	Compd	R_3	R_4	% Z isomer	IC_{50}[a] (μM)
Ox1	H	H	0	72.1 ± 5.5	**Ox18**	3-Cl	H	0	36.7 ± 1.7
Ox2	4-CH_3	H	0	113.3 ± 10.0	**Ox19**	2-Cl	H	0	75.4 ± 5.8
Ox3	3-CH_3	H	0	99.3 ± 7.8	**Ox20**	4-Br	H	0	>250
Ox4	2-CH_3	H	0	144.3 ± 10.8	**Ox21**	3-Br	H	0	102.9 ± 7.4
Ox5	4-CH_3CH_2	H	0	>250	**Ox22**	2-Br	H	0	67.1 ± 5.0
Ox6	4-$(CH_3)_2CH$	H	0	>250	**Ox23**	2,4-diCl	H	100	122.4 ± 11.6
Ox7	4-$(CH_3)_3C$	H	0	>250	**Ox24**	2,3-diCl	H	0	156.8 ± 13.4
Ox8	4-CH_3O	H	0	73.4 ± 5.7	**Ox25**[b]	–	H	100	>250
Ox9	3-CH_3O	H	0	90.6 ± 8.5	**Ox26**	4-OH	H	0	>250
Ox10	2-CH_3O	H	0	56.7 ± 8.4	**Ox27**	3-OH	H	0	>250
Ox11	4-CH_3CH_2O	H	0	114.5 ± 9.3	**Ox28**	2-OH	H	100	>250
Ox12	2-CH_3CH_2O	H	0	156.2 ± 14.9	**Ox29**	3-Cl	F	47	97.8 ± 6.6
Ox13	4-CF_3	H	43	62.8 ± 4.4	**Ox30**	3-Cl	Cl	65	157.9 ± 14.1
Ox14	2-CF_3	H	0	89.5 ± 7.8	**Ox31**	3-Cl	Br	73	>250
Ox15	4-F	H	0	89.3 ± 8.3	**Ox32**	3-Cl	CH_3	0	87.4 ± 7.0
Ox16	2-F	H	0	87.3 ± 5.8	**Ox33**[b]	–	H	–	43.6 ± 6.7
Ox17	4-Cl	H	0	120.8 ± 9.8					

[a] Note: All 50% inhibition concentration (IC_{50}) values are presented as the means ± SD (n = 4), μM.
[b] For compd **Ox25** and **33**, the substituent on 3-position of indolin-2-one ring is 2'-naphthyl and methylene group, respectively.

one **Ox1**.

Before the next exploration, we performed the cytotoxicity experiments (vide infra) for the potent compounds in different classes with the hope of pursuing a compound with desirable selectivity in the following optimization. Compound **Py25** was preferable since its high activity and low cytotoxicity against HepG2 cells and human hepatic L02 cells. The nitrogen atom of **Py25** was modified by alkyl groups with different chain length ranging from 4 to 16. Among these analogues, **Py38** presented a ~1.5-fold decrease in activity while others suffered a significant loss (see Table 5). In addition, the benzyl substitution led to a more potent compound **Py43**, with IC_{50} value of 38.2 μM. Then, we varied the substitution around the benzene ring using different commercially available benzyl bromides. Consequently, 2, 6-dichlorobenzylbromide provided the most potent analogue **Py51** (IC_{50} = 10.4 μM) in our hand. Further comparisons between the N-substituted α-methylene-γ-lactams (**La1-3**) and their corresponding N-substituted **Py25** analogues were performed (see Table 5). There was no apparent increase in activity for N-substituted α-methylene-γ-lactams, shedding light on the role of the phenyl groups on the *exo*-methylene of the γ-lactam scaffold.

Table 5
The 50% inhibition concentration (IC_{50}) of compounds **Py38**–**51** and **La1-3** against spore germination of *C. lagenarium*.

Compd	R_5	IC_{50}[a] (μM)
Py38	$CH_3(CH_2)_3$	64.9 ± 4.1
Py39	$CH_3(CH_2)_4$	78.2 ± 8.0
Py40	$(CH_3)_2CH(CH_2)_2$	106.8 ± 12.1
Py41	$CH_3(CH_2)_9$	>250
Py42	$CH_3(CH_2)_{15}$	>250
Py43	$C_6H_5CH_2$	38.2 ± 4.9
Py44	4-$FC_6H_4CH_2$	34.4 ± 4.8
Py45	4-$ClC_6H_4CH_2$	28.1 ± 4.1
Py46	4-$BrC_6H_4CH_2$	40.8 ± 2.6
Py47	4-$CH_3C_6H_4CH_2$	37.5 ± 3.4
Py48	3-$ClC_6H_4CH_2$	20.6 ± 3.5
Py49	3-$FC_6H_4CH_2$	39.7 ± 3.0
Py50	2-$FC_6H_4CH_2$	18.2 ± 3.9
Py51	2,6-di$ClC_6H_3CH_2$	10.4 ± 1.7
La1	$C_6H_5CH_2$	85.6 ± 8.2
La2	4-$ClC_6H_4CH_2$	79.2 ± 13.5
La3	4-$CH_3C_6H_4CH_2$	120.5 ± 10.4

[a] Note: All 50% inhibition concentration (IC_{50}) values are presented as the means ± SD (n = 4), μM.

2.3. Cytotoxicity

In the process of scaffold optimization, the cytotoxicity and selectivity were comprehensively considered. The cytotoxicity of the highly potent compounds in each class was assessed evaluated in HepG2 cells and human hepatic L02 cells (see Table 6). Either the *N*-unsubstituted or the N-substituted α-arylidene-γ-lactams were generally less toxic to HepG2 cells and human hepatic L02 cells, emphasizing a good selectivity. This finding was in agreement with the previous report for α-arylidene-γ-lactones where induction of the appropriate substituents on the α-arylidene group could reduce their toxicity [34–36]. For the α-arylidene-δ-lactams, their cytotoxicity is as comparative as their antifungal activity while being less efficient. Albeit 3-benzylideneindolin-2-ones were equipped with high antifungal activity, their nonnegligible cytotoxicity led to a poor selectivity. Beside the HepG2 cells and human hepatic L02 cells, 3-benzylideneindolin-2-ones had reported cytotoxicity against human cancer cell lines MCF-7 and HCT116 [48]. Summarizing, the *N*-benzyl substituted analogues possessed good selectivity together with excellent antifungal activity, suggesting a preferable natural-based scaffold for further lead optimization.

2.4. The ultrastructural change studies

In the primary infection of diseases cycle, the germinated spores produced the germ tube which might improve the adherence to host cells and penetration into the host. Therefore, blocking the spore germination and germ tube growth has a pivotal role in the control of plant diseases. Apart from inhibition of spore germination, compound **Py51** was observed to inhibit the germ tube growth. TEM was used to determine ultrastructural changes of germ tubes induced by **Py51**. The results may lay a foundation for the further antifungal mechanism studies on this natural-based scaffold.

Control cells were featured with the well-defined cytoplasmic integrity intact (Fig. 4 **A, B**). The visible cytoplasmic membrane showed good adhesion to cell wall that appeared as a bright, fibrous layer. Various identifiable organelles distinct in their constituent elements, and normal size vacuoles were observed in cells. The cell nuclei surrounded by the nuclear membranes, and electron-dense nucleoli were visible in many cases. The numerous mitochondria with membranous cristae were visibly presented. Many of them were located in the apical region of growing germ tubes to supply energy for elongation, indicating that the cells were growing rapidly.

Compared with the control, the treated cells revealed an abnormal subcellular morphology (Fig. 4 C-F). After 12 h of treatment, the fungal cells have already showed some alternations of the inner membranes that became irregular in thickness and density. Although internal organelles like mitochondria were well preserved, they witnessed an aberrant morphology characterized by an abnormality in the size of individual mitochondria and a concomitant increase in the number. Vacuoles swelled in irregular shape. After 24 h of treatment, many cells were damaged, showing thickening cell wall, cytoplasm membrane detachment integratedly from cell wall, invaginations of cytoplasm membrane, occurrence of numerous vacuoles, and mitochondrial membrane discontinuity or disappearance. When treatment was prolonged up to 48 h, cytoplasm was clearly degenerated due to the high vacuolization and organelles were not recognized any more. At 72 h, a large part of the fungal structures was disrupted, and many cells looked empty.

Taken together, a remarkable ultrastructural change was observed for mitochondria encompassing the abnormality in the size and number of mitochondria in 12 h and mitochondrial membrane discontinuity or disappearance in 24 h. As is known, mitochondria perform pivotal functions essential for ATP production, homeostasis, and metabolism. The alternations in the size and number of mitochondria might be subjected to the disruption of mitochondrial functions during the early stage. After a long period of treatment, the mitochondria suffered a seriously disruptive damage, leading to the membrane discontinuity or disappearance. These results revealed that the mitochondria appeared one of the primary targets.

Table 6
Cytotoxicity activity against HepG2 and human hepatic L02 cell lines.

Compd	IC_{50} (μM)	
	HepG2	human hepatic L02
Py1	197.5	154.4
Py2	170.2	207.3
Py20	135.0	156.9
Py25	125.3	179.2
Py29	64.9	60.8
Py45	96.8	131.5
Py48	108.7	239.6
Py50	134.2	143.6
Py51	141.2	161.2
La2	133.9	73.3
Pi1	485.2	201.9
Pi17	192.7	119.3
Pi23	263.8	118.5
Ox1	5.4	19.7
Ox10	10.1	22.4
Ox13	2.7	3.4
Ox18	22.5	18.8
Ox33	26.1	53.0

3. Conclusion

In this study, 62 new and 59 known natural α-methylenelactam analogues including α-methylene-γ-lactams, α-arylidene-γ and δ-lactams, and 3-arylideneindolin-2-ones were synthesized and investigated for their antifungal activity. Bioassay results indicated that most of the α-arylidene-γ-lactams possessed superior activity over the α-arylidene-γ-lactams and better selectivity than 3-arylideneindolin-2-ones. Compound **Py51** possessed the highest antifungal activity against *C. orbiculare* with $IC_{50} = 10.4$ μM but poor cytotoxic activity with $IC_{50} = 141.2$ μM (against HepG2 cell line) and 161.2 μM (against human hepatic L02 cell line). Ultrastructural changes studies showed that **Py51** could cause important cell morphological changes in *C. orbiculare*, such as plasma membrane detached from cell wall, cell wall thickening, mitochondria disruption, a dramatic increase in vacuolation, and eventually a complete loss in the integrity of organelles. Significantly, mitochondria appeared one of the primary targets, as confirmed by their remarkably aberrant morphological changes. Further structural optimization is still well ongoing with the aim of discovering and developing improved natural-based crop-protection agents.

4. Experimental section

4.1. General

All the starting materials, reagents, and solvents were obtained from commercial sources and used without further purification unless otherwise stated. The reaction solvents were distilled prior to use. Tetrahydrofuran (THF), diethyl ether (Et_2O) and toluene were distilled from sodium and benzophenone under an Ar atmosphere. Dimethylformamide (DMF), triethylamine (Et_3N), diisopropylamine and dichloromethane (DCM) were distilled from

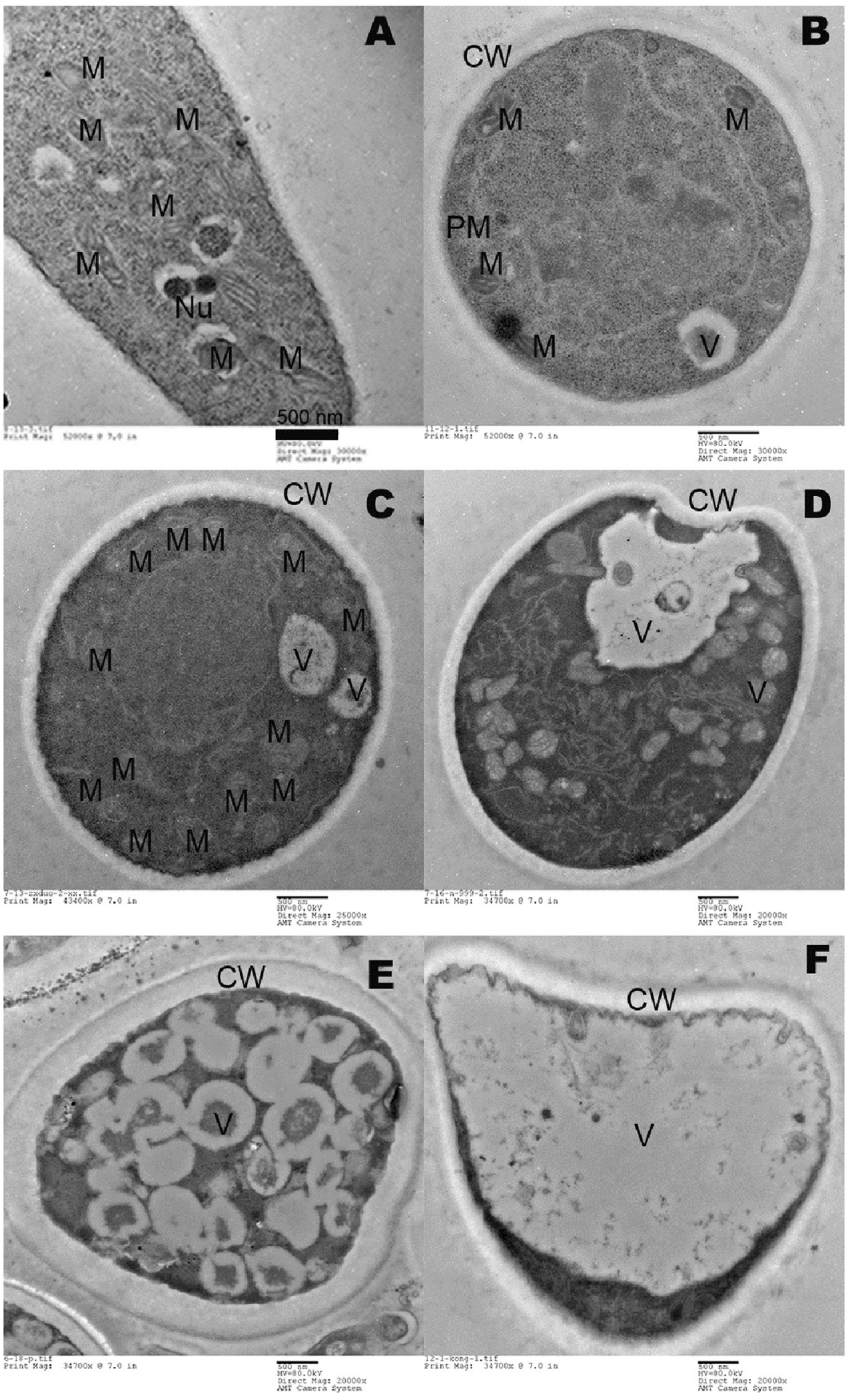


Fig. 4. Ultrastructural morphological images of germinated *C. orbiculare* spores treated or not with compound **Py51**. **A**-**B**, Control; **C,** 12 h; **D**, 24 h; **E,** 48 h; **F,** 72 h. CW, cell wall; Nu, nucleolus; PM, plasma membrane; M, mitochondria; V, vacuole.

calcium hydride and stored in 4 Å molecular sieves. Generally, all reactions were carried out using standard air-free and moisture-free techniques under an inert nitrogen atmosphere with dry solvents unless otherwise stated. Reaction progress was monitored by thin layer chromatography (TLC) using GF254 silica gel with fluorescent indicator on glass plates. Visualization was achieved with UV light and Dragendorff's reagent unless otherwise stated. Chromatography was performed using Qingdao Haiyang silica gel (200–300 mesh). ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Bruker AMX500 (^{1}H at 500 MHz, ^{13}C at 125 MHz) magnetic resonance spectrometer. ^{1}H chemical shifts were reported in ppm using residual $CHCl_3$ (δ 7.26) and DMSO-d_6 (δ 2.50) as internal standards. Spin multiplicities are described as br (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants (J) were reported in Hertz (Hz). Proton decoupled ^{13}C NMR spectra were reported in ppm (δ) relative to residual $CHCl_3$ (δ 77.0) and DMSO (39.5).

4.2. Synthesis

4.2.1. General procedure for synthesis of N-propylcinnamamide [54]

Propan-1-amine (0.9 eq) and 4-dimethylaminopyridine (DMAP)

(1.0 eq) were added to a stirred solution of cinnamic acid (1.0 eq) in anhydrous DCM. After the reaction mixture was cooled in an ice bath, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl) (1.0 eq) was added. After stirring for 24 h, the reaction mixture was washed with a saturated brine solution and water. The residual organic layer was dried by Na_2SO_4 and then purified by silica gel chromatography and eluted with petroleum ether/EtOAc (10/3) to yield pure *N*-propylcinnamamide as a white solid. Yield: 85%; m.p.: 82–83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.61 (d, J = 15.6 Hz, 1H), 7.44–7.46 (m, 2H), 7.29–7.30 (m, 3H), 6.48 (d, J = 15.7 Hz, 1H), 6.32 (br, 1H), 3.32–3.36 (m, 2H), 1.55–1.62 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 166.2, 140.6, 135.0, 129.5, 128.8, 127.7, 121.2, 41.5, 22.9, 11.5; ESI-MS: *m/z* 212.1 ($[M+Na]^+$).

4.2.2. General procedure for synthesis of α-methylene-γ-lactam (**1**) [39,40]

4.2.2.1. N-boc-2-pyrrolidone. To a solution of 2-pyrrolidinone (8.51 g, 100 mmol, 1.0 eq) in DCM (200 mL) were added DMAP (12.2 g, 100 mmol, 1.0 eq), Et_3N (13.8 mL, 100 mmol, 1.0 eq), di-*tert*-butyl dicarbonate (Boc_2O) (43.65 g, 200 mmol, 2.0 eq). CO_2 was released from the stirring solution. The reaction mixture was stirred at room temperature for 12 h. The solvent was then evaporated under reduced pressure and the residual product was purified by silica gel chromatography (petroleum ether/EtOAc = 4/1) to afford *N*-boc-2-pyrrolidone as a white solid. Yield: 86%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 3.72 (t, J = 7.0 Hz, 2H), 2.48 (t, J = 8.2 Hz, 2H), 1.94–2.01 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 174.3, 150.2, 82.7, 46.5, 32.9, 28.0, 17.4; ESI-MS: *m/z* 208.1 ($[M+Na]^+$).

4.2.2.2. α-Methylene-γ-lactam. Diethyl oxalate (7.3 g, 50 mmol, 2.0 eq) and sodium hydride (1.2 g, 30 mmol, 1.2 eq) were added to diethyl ether (20 mL) and stirred at 40 °C. A solution of *N*-boc-2-pyrrolidone (4.6 g, 25 mmol, 1.0 eq) in 20 mL diethyl ether was added dropwise over a period of 1 h, and the mixture was stirred at 40 °C for 2 days. After that, the sodium salt was filtered from the resulting yellow solution, washed with diethyl ether and redissolved in DMF. Paraformaldehyde (1.5 g, 50 mmol, 2.0 eq) was added and the reaction mixture was heated to 100 °C for 1.5 h. After cooling, the reaction mixture was filtered, dried and concentrated under reduced pressure to give a yellow oil residue. The above oil product (2.0 g, 10 mmol) was added to a stirred DCM solution (20 mL) at room temperature. Trifluoroacetic acid (2 mL) was added to the solution and the stirring was continued for 0.5 h. Finally, the reaction mixture was concentrated, which was followed by addition of DCM (20 mL) and concentration (×4). Purification was subsequently performed by column chromatography on silica gel, yielding α-methylene-γ-lactam. Yield: 16%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 6.03 (t, J = 2.8 Hz, 1H), 5.45 (t, J = 2.5 Hz, 1H), 3.44–3.50 (m, 2H), 2.77–2.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 167.9, 139.6, 115.7, 43.5, 23.9. ESI-MS: *m/z* 98.1 ($[M+H]^+$).

4.2.3. General procedure for synthesis of α-alkenyl-γ-lactams (**Py1-40**) and α-alkenyl-δ-lactams (**Pi1-32**) [43]

2-Pyrrolidinone or 2-piperidinone (11 mmol, 1.1 eq) was dissolved in dry toluene (5 mL). To this solution, trifluoroacetic anhydride (TFAA) (2.5 g, 12 mmol, 1.2eq) was charged slowly by a syringe at 5 °C. Upon complete addition, the solution was stirred for 1 h at room temperature. Toluene was removed under vacuum using a rotary evaporator. After evaporation, another portion of toluene (10 mL) was added to the concentrate and again removed under vacuum, which was repeated twice. The resulting pale yellow liquid was then mixed with corresponding substituted benzaldehyde (10 mmol, 1.0 eq) and the homogeneous solution in a syringe was slowly injected to a 1 M solution of potassium *t*-butoxide (KO_tBu) in THF (13 mL, 13 mmol, 1.3 eq) at 0 °C. Once complete addition, the mixture was heated to 55 °C and stirred therein for 1 h. Then the reaction mixture was concentrated to a thick slurry. To the concentrate with vigorous stirring, water (100 mL) was added slowly to precipitate the crude product. The water solution with precipitate was cooled to 5 °C and held therein for 1 h. The solution was filtered, and the solid was washed with water, and dried in vacuum oven overnight. The dried crude product was purified by recrystallization from petroleum ether/EtOAc.

*4.2.3.1. (E)-3-benzylidenepyrrolidin-2-one (**Py1**) [55].* Light yellow solid; yield: 45%; mp: 102–103 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.14 (br, 1H), 7.32–7.54 (m, 5H), 7.09 (t, J = 2.5 Hz, 1H), 3.36 (t, J = 6.5 Hz, 2H), 3.06 (td, J = 6.3, 2.4 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.5, 135.6, 132.6, 129.2, 128.7, 128.2, 127.7, 38.7, 25.8; HR-MS (ESI): *m/z* calcd for $C_{11}H_{11}NONa$ ($[M+Na]^+$) 196.0733, found 196.0735.

*4.2.3.2. (E)-3-(4-methylbenzylidene)pyrrolidin-2-one (**Py2**) [56].* White solid; yield: 47%; mp: 104–105 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.08 (br, 1H), 7.23–7.42 (m, 4H), 7.05 (t, J = 2.5 Hz, 1H), 3.36 (t, J = 6.5 Hz, 2H), 3.03 (td, J = 6.3, 2.4 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.6, 137.8, 132.8, 131.4, 129.3, 129.2, 127.6, 38.7, 25.8, 20.8; HR-MS (ESI): *m/z* calcd for $C_{12}H_{13}NONa$ ($[M+Na]^+$) 210.0889, found 210.0893.

*4.2.3.3. (E)-3-(3-methylbenzylidene)pyrrolidin-2-one (**Py3**).* Light yellow solid; yield: 37%; mp: 101–102 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.10 (br, 1H), 7.15–7.33 (m, 4H), 7.04 (t, J = 2.8 Hz, 1H), 3.36 (t, J = 6.2 Hz, 2H), 3.03 (td, J = 6.5, 2.7 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.5, 137.8, 135.5, 132.3, 129.8, 128.9, 128.5, 127.7, 126.3, 38.6, 25.8, 20.9; HR-MS (ESI): *m/z* calcd for $C_{12}H_{13}NONa$ ($[M+Na]^+$) 210.0889, found 210.0893.

*4.2.3.4. (E)-3-(2-methylbenzylidene)pyrrolidin-2-one (**Py4**).* Light yellow solid; yield: 35%; mp: 104–105 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.13 (br, 1H), 7.23–7.47 (m, 5H), 3.33 (t, J = 6.5 Hz, 2H), 2.97 (td, J = 6.8, 2.8 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.4, 136.9, 134.2, 133.1, 130.2, 128.0, 127.6, 125.9, 125.1, 38.7, 25.5, 19.4; HR-MS (ESI): *m/z* calcd for $C_{12}H_{13}NONa$ ($[M+Na]^+$) 210.0889, found 210.0893.

*4.2.3.5. (E)-3-(4-ethylbenzylidene)pyrrolidin-2-one (**Py5**).* White solid; yield: 49%; mp: 109–111 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.09 (br, 1H), 7.26–7.45 (m, 4H), 7.05 (t, J = 2.5 Hz, 1H), 3.36 (t, J = 6.5 Hz, 2H), 3.03 (td, J = 6.4, 2.4 Hz, 2H), 2.62 (q, J = 7.6 Hz, 2H), 1.18 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.6, 144.1, 133.2, 131.5, 129.3, 128.1, 127.6, 38.7, 27.9, 25.7, 15.4; HR-MS (ESI): *m/z* calcd for $C_{13}H_{15}NONa$ ($[M+Na]^+$) 224.1046, found 224.1049.

*4.2.3.6. (E)-3-(4-isopropylbenzylidene)pyrrolidin-2-one (**Py6**).* White solid; yield: 43%; mp: 113–115 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.08 (br, 1H), 7.29–7.46 (m, 4H), 7.05 (t, J = 2.6 Hz, 1H), 3.36 (t, J = 6.4 Hz, 2H), 3.03 (td, J = 6.6, 2.4 Hz, 2H), 2.86–2.94 (m, 1H), 1.20 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.6, 148.6, 133.2, 131.5, 129.3, 127.6, 126.6, 38.6, 33.2, 25.7, 23.6; HR-MS (ESI): *m/z* calcd for $C_{14}H_{17}NONa$ ($[M+Na]^+$) 238.1202, found 238.1205.

*4.2.3.7. (E)-3-(4-(tert-butyl)benzylidene)pyrrolidin-2-one (**Py7**).* White solid; yield: 47%; mp: 112–113 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.10 (br, 1H), 7.43–7.47 (m, 4H), 7.06 (t,

J = 2.9 Hz, 1H), 3.36 (t, J = 6.4 Hz, 2H), 3.03 (td, J = 6.5, 2.8 Hz, 2H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 171.1, 151.3, 133.3, 132.1, 129.6, 128.0, 126.0, 39.2, 34.9, 31.4, 26.2; HR-MS (ESI): m/z calcd for $C_{15}H_{19}NONa$ ([M+Na]$^+$) 252.1359, found 252.1361.

*4.2.3.8. (E)-3-(4-methoxybenzylidene)pyrrolidin-2-one (**Py8**) [56].* Light yellow solid; yield: 51%; mp: 121–122 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.02 (br, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.03 (t, J = 2.7 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 3.78 (s, 3H), 3.36 (t, J = 6.4 Hz, 2H), 3.02 (td, J = 6.5, 2.4 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.7, 159.2, 130.8, 129.7, 128.2, 127.4, 114.2, 55.1, 38.6, 25.7; HR-MS (ESI): m/z calcd for $C_{12}H_{13}NO_2Na$ ([M+Na]$^+$) 226.0838, found 226.0839.

*4.2.3.9. (E)-3-(3-methoxybenzylidene)pyrrolidin-2-one (**Py9**).* Light yellow solid; yield: 31%; mp: 119–121 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.12 (br, 1H), 7.34 (m, 1H), 6.91–7.11 (m, 4H), 3.78 (s, 3H), 3.36 (t, J = 6.2 Hz, 2H), 3.06 (td, J = 6.5, 2.7 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.9, 159.8, 137.5, 133.4, 130.2, 128.2, 122.1, 115.0, 114.5, 55.5, 39.2, 26.2; HR-MS (ESI): m/z calcd for $C_{12}H_{13}NO_2Na$ ([M+Na]$^+$) 226.0838, found 226.0839.

*4.2.3.10. (E)-3-(2-methoxybenzylidene)pyrrolidin-2-one (**Py10**).* Light yellow solid; yield: 34%; mp: 117–118 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.07 (br, 1H), 7.31–7.48 (m, 3H), 7.05 (d, J = 8.3 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 3.83 (s, 3H), 3.33 (t, J = 6.3 Hz, 2H), 2.99 (td, J = 6.5, 2.7 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.9, 159.8, 137.5, 133.4, 130.2, 128.2, 122.1, 115.0, 114.5, 55.5, 39.2, 26.2; HR-MS (ESI): m/z calcd for $C_{12}H_{13}NO_2Na$ ([M+Na]$^+$) 226.0838, found 226.0839.

*4.2.3.11. (E)-3-(4-ethoxybenzylidene)pyrrolidin-2-one (**Py11**) [57].* White solid; yield: 48%; mp: 141–144 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.03 (br, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.03 (t, J = 2.7 Hz, 1H), 6.97 (d, J = 8.6 Hz, 2H), 4.04 (q, J = 7.0 Hz, 2H), 3.35 (t, J = 6.2 Hz, 2H), 3.00 (td, J = 7.0, 2.5 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 171.3, 159.0, 131.3, 130.1, 128.6, 128.0, 115.1, 36.6, 39.1, 26.1, 15.0; HR-MS (ESI): m/z calcd for $C_{13}H_{15}NO_2Na$ ([M+Na]$^+$) 240.0995, found 240.0995.

*4.2.3.12. (E)-3-(2-ethoxybenzylidene)pyrrolidin-2-one (**Py12**).* Light yellow solid; yield: 38%; mp: 134–136 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.09 (br, 1H), 7.28–7.48 (m, 3H), 7.03 (d, J = 8.5 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 4.07 (q, J = 6.7 Hz, 2H), 3.33 (t, J = 6.4 Hz, 2H), 2.99 (td, J = 6.3, 2.7 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 171.2, 157.1, 132.5, 130.2, 129.0, 124.7, 122.6, 120.7, 112.5, 64.0, 39.2, 26.3, 15.1; HR-MS (ESI): m/z calcd for $C_{13}H_{15}NO_2Na$ ([M+Na]$^+$) 240.0995, found 240.0995.

4.2.3.13. 4-Butoxybenzaldehyde (4a) [58]. In a 100 mL round bottomed flask equipped with a reflux condenser and a magnetic stirring bar were dissolved 4-hydroxybenzaldehyde (35 g, 287 mmol) and 1-bromobutane (30.92 mL, 287 mmol) in DMF (750 mL). The mixture then was stirred under nitrogen for 20 min. Anhydrous potassium carbonate (118.83 g, 860 mmol) was then added and the mixture was stirred and heated at 70 °C under nitrogen. After 20 h, the reaction was allowed to cool to room temperature, treated with excess water, and extracted with ethyl acetate. The combined organic extracts were then washed with water several times and dried over anhydrous sodium sulfate, filtered. The crude product was purified by chromatography (PE/EA, 20/1) yielding a brown oil. Yield: 95%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.89 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.6 Hz, 2H), 4.06 (t, J = 6.3 Hz, 2H), 1.79–1.85 (m, 2H), 1.49–1.57 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 190.7, 164.2, 131.9, 129.8, 114.7, 68.1, 31.0, 19.1, 13.7; ESI-MS: m/z 179.2 ([M+H$^+$]); The following alkoxy benzaldehyde derivatives **4b-h** were synthesized in a similar method.

*4.2.3.14. (E)-3-(4-butoxybenzylidene)pyrrolidin-2-one (**Py13**).* White solid; yield: 41%; mp: 151–153 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.00 (br, 1H), 7.45 (d, J = 7.9 Hz, 2H), 6.97–7.03 (m. 3H), 3.99 (t, J = 6.3 Hz, 2H), 3.35 (t, J = 6.2 Hz, 2H), 3.01 (td, J = 7.0, 2.5 Hz, 2H), 1.67–1.70 (m, 2H), 1.41–1.44 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 171.3, 159.2, 131.3, 130.1, 128.6, 128.0, 115.1, 67.7, 39.1, 31.1, 26.2, 19.2, 14.1; HR-MS (ESI): m/z calcd for $C_{15}H_{19}NO_2Na$ ([M+Na]$^+$) 268.1308, found 268.1310.

*4.2.3.15. 2-Butoxybenzaldehyde (**4b**) [59].* Brown oil; yield: 91%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 10.49 (s, 1H), 7.78–7.90 (m, 1H), 7.47–7.49 (m, 1H), 6.95–6.96 (m, 2H), 4.04 (t, J = 6.3 Hz, 2H), 1.79–1.80 (m, 2H), 1.49–1.52 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 189.7, 161.5, 135.8, 128.0, 124.8, 120.3, 112.6, 68.1, 31.0, 19.2, 13.7; ESI-MS: m/z 179.2 ([M+H$^+$]).

*4.2.3.16. (E)-3-(2-butoxybenzylidene)pyrrolidin-2-one (**Py14**).* White solid; yield: 29%; mp: 147–148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.78 (t, J = 2.7 Hz, 1H), 7.45–7.46 (m, 1H), 7.30–7.33 (m, 1H), 7.17 (br, 1H), 6.94–7.01 (m, 2H), 4.05 (t, J = 6.6 Hz, 2H), 3.55 (t, J = 6.4 Hz, 2H), 3.12 (td, J = 6.5, 2.6 Hz, 2H), 1.83–1.89 (m, 2H), 1.51–1.58 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 157.6, 130.2, 129.8, 128.9, 125.2, 125.0, 120.0, 111.9, 68.2, 39.7, 31.2, 26.6, 19.3, 13.8; HR-MS (ESI): m/z calcd for $C_{15}H_{19}NO_2Na$ ([M+Na]$^+$) 268.1308, found 268.1310.

*4.2.3.17. 4-(Isopentyloxy)benzaldehyde (**4c**) [60].* Brown oil; yield: 92%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.89 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.6 Hz, 2H), 4.09 (t, J = 6.4 Hz, 2H), 1.82–1.90 (m, 1H), 1.70–1.75 (m, 2H), 1.00 (d, J = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 190.7, 164.2, 131.9, 129.8, 114.7, 66.8, 37.7, 25.0, 22.5; ESI-MS: m/z 193.3 ([M+H$^+$]).

*4.2.3.18. (E)-3-(4-(isopentyloxy)benzylidene)pyrrolidin-2-one (**Py15**).* White solid; yield: 54%; mp: 141–142 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.00 (br, 1H), 7.45 (d, J = 7.9 Hz, 2H), 6.98–7.03 (m. 3H), 4.02 (t, J = 6.3 Hz, 2H), 3.35 (t, J = 6.2 Hz, 2H), 3.01 (td, J = 7.0, 2.5 Hz, 2H), 1.73–1.80 (m, 1H), 1.59–1.63 (m, 2H), 0.92 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm):159.1, 131.3, 130.1, 128.6, 128.0, 115.2, 66.4, 39.1, 37.8, 26.1, 25.0, 22.9; HR-MS (ESI): m/z calcd for $C_{16}H_{21}NO_2Na$ ([M+Na]$^+$) 282.1465, found 282.1466.

*4.2.3.19. 2-(Isopentyloxy)benzaldehyde (**4d**) [59].* Brown oil; yield: 98%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 10.54 (s, 1H), 7.85–7.86 (m, 1H), 7.54–7.57 (m, 1H), 7.01–7.04 (m, 2H), 4.14 (t, J = 6.5 Hz, 2H), 1.85–1.94 (m, 1H), 1.76–1.80 (m, 2H), 1.00 (d, J = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 189.8, 161.5, 135.9, 128.2, 124.9, 120.4, 112.5, 66.9, 37.7, 25.1, 22.5; ESI-MS: m/z 193.3 ([M+H$^+$]).

*4.2.3.20. (E)-3-(2-(isopentyloxy)benzylidene)pyrrolidin-2-one (**Py16**).* White solid; yield: 39%; mp: 135–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.78 (t, J = 2.7 Hz, 1H), 7.45–7.46 (m, 1H), 7.30–7.33 (m, 1H), 7.07 (br, 1H), 6.95–7.01 (m, 2H), 4.07 (t, J = 6.6 Hz, 2H), 3.55 (t, J = 6.4 Hz, 2H), 3.12 (td, J = 6.5, 2.6 Hz, 2H), 1.85–1.93 (m, 1H), 1.75–1.80 (m, 2H), 1.00 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 172.8, 157.6, 130.1, 129.8, 128.9, 125.3, 125.0, 120.0, 111.8, 67.0, 39.7, 37.9, 26.6, 25.1, 22.6; HR-MS (ESI): m/z calcd for $C_{16}H_{21}NO_2Na$ ([M+Na]$^+$) 282.1465, found 282.1466.

4.2.3.21. 4-(Dodecyloxy)benzaldehyde (4e) [61]. Brown oil; yield: 97%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.89 (s, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.6 Hz, 2H), 4.05 (t, J = 6.6 Hz, 2H), 1.80–1.86 (m, 2H), 1.45–1.51 (m, 2H), 1.29–1.39 (m, 16H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 190.6, 164.2, 131.9, 129.8, 114.7, 68.4, 31.9, 29.6, 29.6, 29.5, 29.5, 29.3, 29.0, 25.9, 22.6, 14.1; ESI-MS: m/z 291.4 ([M+H$^+$]).

*4.2.3.22. (E)-3-(4-(dodecyloxy)benzylidene)pyrrolidin-2-one (**Py17**).* White solid; yield: 42%; mp: 165–167 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.46 (d, J = 6.7 Hz, 2H), 7.34 (t, J = 2.9 Hz, 1H), 6.96 (d, J = 8.6 Hz, 2H), 4.02 (t, J = 6.5 Hz, 2H), 3.58 (t, J = 6.6 Hz, 2H), 3.17 (td, J = 7.0, 2.5 Hz, 2H), 1.79–1.85 (m, 2H), 1.46–1.52 (m, 2H), 1.29–1.39 (m, 16H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 159.5, 131.1, 130.2, 128.2, 127.1, 114.7, 68.1, 39.5, 31.9, 29.6, 29.6, 29.6, 29.5, 29.3, 29.3, 29.2, 26.3, 26.0, 22.7; HR-MS (ESI): m/z calcd for $C_{23}H_{35}NO_2Na$ ([M+Na]$^+$) 380.2560, found 380.2564.

*4.2.3.23. 2-(Dodecyloxy)benzaldehyde (**4f**)* [62]. Brown oil; yield: 93%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 10.5 (s, 1H), 7.83–7.85 (m, 1H), 7.52–7.55 (m, 1H), 6.98–7.02 (m, 2H), 4.09 (t, J = 6.4 Hz, 2H), 1.80–1.86 (m, 2H), 1.48–1.52 (m, 2H), 1.29–1.39 (m, 16H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 189.7, 161.5, 135.8, 128.1, 124.9, 120.4, 112.5, 31.9, 29.6, 29.6, 29.6, 29.5, 29.3, 29.1, 26.0, 22.7, 14.1; ESI-MS: m/z 291.4 ([M+H$^+$]).

*4.2.3.24. (E)-3-(2-(dodecyloxy)benzylidene)pyrrolidin-2-one (**Py18**).* White solid; yield: 36%; mp: 152–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.78 (t, J = 2.7 Hz, 1H), 7.45–7.46 (m, 1H), 7.30–7.33 (m, 1H), 6.94–7.01 (m, 2H), 4.03 (t, J = 6.6 Hz, 2H), 3.55 (t, J = 6.4 Hz, 2H), 3.12 (td, J = 6.5, 2.6 Hz, 2H), 1.84–1.89 (m, 2H), 1.46–1.52 (m, 2H), 1.30–1.38 (m, 16H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 173.0, 157.6, 130.4, 129.7, 128.9, 125.1, 125.1, 120.0, 111.9, 68.6, 39.8, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 26.6, 26.0, 22.7, 14.1; HR-MS (ESI): m/z calcd for $C_{23}H_{35}NO_2Na$ ([M+Na]$^+$) 380.2560, found 380.2564.

*4.2.3.25. 4-(Benzyloxy)benzaldehyde (**4g**)* [63]. White solid; yield: 91%; mp: 70–71 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.93 (s, 1H), 7.87–7.89 (m, 2H), 7.38–7.49 (m, 5H), 7.11–7.13 (m, 2H), 5.19 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 190.7, 163.7, 136.0, 132.0, 130.2, 128.7, 128.3, 127.5, 115.2, 70.3; ESI-MS: m/z 213.0 ([M+H$^+$]).

*4.2.3.26. (E)-3-(4-(benzyloxy)benzylidene)pyrrolidin-2-one (**Py19**).* White solid; yield: 49%; mp: 133–135 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.04 (br, 1H), 7.34–7.51 (m, 7H), 7.07–7.11 (m, 3H), 5.17 (s, 2H), 3.38 (t, J = 6.3 Hz, 2H), 3.04 (td, J = 6.4, 2.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 171.3, 158.8, 137.3, 131.3, 130.4, 128.9, 128.9, 128.3, 128.1, 127.9, 115.5, 69.7, 39.1, 26.1; HR-MS (ESI): m/z calcd for $C_{18}H_{17}NO_2Na$ ([M+Na]$^+$) 302.1151, found 302.1155.

*4.2.3.27. 2-(Benzyloxy)benzaldehyde (**4h**)* [64]. White solid; yield: 97%; mp: 49–51 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 10.06 (s, 1H), 7.90–7.92 (m, 1H), 7.38–7.59 (m, 6H), 7.06–7.11 (m, 2H), 5.22 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 189.7, 161.1, 136.1, 135.9, 128.7, 128.4, 128.3, 127.3, 125.2, 121.0, 113.1, 70.5; ESI-MS: m/z 213.0 ([M+H$^+$]).

*4.2.3.28. (E)-3-(2-(benzyloxy)benzylidene)pyrrolidin-2-one (**Py20**).* White solid; yield: 42%; mp: 142–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.78 (t, J = 2.7 Hz, 1H), 7.27–7.49 (m, 8H), 6.97–7.04 (m, 2H), 5.17 (s, 2H), 3.54 (t, J = 6.3 Hz, 2H), 3.11 (td, J = 6.4, 2.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 172.8, 157.1, 136.9, 130.7, 129.7, 129.1, 128.6, 127.8, 127.1, 125.4, 125.1, 120.6, 112.6, 7.03, 39.7, 26.6; HR-MS (ESI): m/z calcd for $C_{18}H_{17}NO_2Na$ ([M+Na]$^+$) 302.1151, found 302.1155.

*4.2.3.29. (E)-3-(2-((tert-butyldimethylsilyl)oxy)benzylidene)pyrrolidin-2-one (**Py21**).*
(2-((*tert*-butyldimethylsilyl)oxy)benzaldehyde was prepared according to the reported literature) White solid; yield: 36%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.66 (s, 1H), 7.50–7.57 (m, 2H), 7.32–7.36 (m, 3H), 3.71 (t, J = 6.3 Hz, 2H), 2.93 (td, J = 6.4, 2.5 Hz, 2H), 1.02 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 162.6, 153.3, 141.6, 131.6, 127.5, 125.8, 124.8, 119.0, 116.6, 39.3, 30.6, 25.6, 18.2, −4.3; ESI-MS: m/z 304.5 ([M+H$^+$]).

*4.2.3.30. (E)-3-(2-hydroxybenzylidene)pyrrolidin-2-one (**Py22**).* White solid; yield: 42%; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 9.53 (br, 1H), 8.07 (br, 1H), 7.23–7.26 (m, 3H), 6.95–7.02 (m, 3H), 6.77–6.79 (m, 1H), 3.39 (t, J = 6.4 Hz, 2H), 3.05 (td, J = 6.5, 2.6 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 171.0, 157.9, 137.3, 132.7, 130.1, 128.4, 120.9, 116.2, 115.9, 39.1, 26.3; HR-MS (ESI): m/z calcd for $C_{11}H_{11}NO_2Na$ ([M+Na]$^+$) 212.0682, found 212.0683.

*4.2.3.31. (E)-3-(4-(dimethylamino)benzylidene)pyrrolidin-2-one (**Py23**).* White solid; yield: 46%; mp: 167–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.44 (d, J = 8.8 Hz, 2H), 7.31 (t, J = 2.7 Hz, 1H), 6.76 (d, J = 8.7 Hz, 2H), 6.69 (br, 1H), 3.57 (t, J = 6.6 Hz, 2H), 3.16 (td, J = 6.7, 2.4 Hz, 2H), 3.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 173.4, 150.4, 131.1, 130.8, 124.7, 123.8, 111.9, 40.1, 39.6, 26.4; HR-MS (ESI): m/z calcd for $C_{13}H_{16}N_2ONa$ ([M+Na]$^+$) 239.1155, found 239.1156.

*4.2.3.32. (E)-3-(4-fluorobenzylidene)pyrrolidin-2-one (**Py24**)* [65]. White solid; yield: 35%; mp: 204–205 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.12 (br, 1H), 7.24–7.60 (m, 4H), 7.09 (t, J = 2.5 Hz, 1H), 3.36 (t, J = 6.5 Hz, 2H), 3.03 (td, J = 6.3, 2.4 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.3, 161.6, 132.3, 132.2, 131.4, 126.5, 115.7, 38.6, 25.5; HR-MS (ESI): m/z calcd for $C_{11}H_{10}FNONa$ ([M+Na]$^+$) 214.0639, found 214.0641.

*4.2.3.33. (E)-3-(2-fluorobenzylidene)pyrrolidin-2-one (**Py25**).* White solid; yield: 31%; mp: 184–186 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.26 (br, 1H), 7.25–7.64 (m, 4H), 7.22 (t, J = 2.9 Hz, 1H), 3.36 (t, J = 6.4 Hz, 2H), 3.03 (td, J = 6.4, 2.7 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.5, 160.7, 135.6, 130.8, 129.7, 125.1, 123.7, 119.1, 116.2, 39.2, 26.1; HR-MS (ESI): m/z calcd for $C_{11}H_{10}FNONa$ ([M+Na]$^+$) 214.0639, found 214.0641.

*4.2.3.34. (E)-3-(4-(trifluoromethyl)benzylidene)pyrrolidin-2-one (**Py26**)* [43]. White solid; yield: 39%; mp: 215–216 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.29 (br, 1H), 7.73–7.78 (m, 4H), 7.16 (t, J = 2.7 Hz, 1H), 3.38 (t, J = 6.0 Hz, 2H), 3.10 (td, J = 6.0, 2.3 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.0, 139.6, 135.8, 129.8, 128.0, 126.1, 125.5, 141.1, 38.7, 25.8; HR-MS (ESI): m/z calcd for $C_{12}H_{10}F_3NONa$ ([M+Na]$^+$) 264.0607, found 264.0606.

*4.2.3.35. (E)-3-(2-(trifluoromethyl)benzylidene)pyrrolidin-2-one (**Py27**)* [65]. Light yellow solid; yield: 38%; mp: 211–213 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.39 (br, 1H), 7.66–7.71 (m, 4H), 3.38 (t, J = 6.0 Hz, 2H), 3.03 (td, J = 6.0, 2.3 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.3, 137.3, 134.4, 132.6, 130.1, 128.9, 128.0, 127.7, 125.9, 141.2, 39.2, 25.9; HR-MS (ESI): m/z calcd for $C_{12}H_{10}F_3NONa$ ([M+Na]$^+$) 264.0607, found 264.0606.

*4.2.3.36. (E)-3-(4-chlorobenzylidene)pyrrolidin-2-one (**Py28**)* [65]. White solid; yield: 49%; mp: 235–237 °C; ^{1}H NMR (500 MHz,

DMSO-d_6) δ_H (ppm): 8.17 (br, 1H), 7.47–7.56 (m, 4H), 7.07 (t, J = 2.9 Hz, 1H), 3.37 (t, J = 6.2 Hz, 2H), 3.04 (td, J = 6.5, 2.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.2, 134.5, 133.5, 132.6, 130.9, 128.6, 126.3, 38.6, 25.6; HR-MS (ESI): *m/z* calcd for $C_{11}H_{10}ClNONa$ ([M+Na]$^+$) 230.0343, found 230.0348.

*4.2.3.37. (3Z,4Z)-3,4-bis(3-chlorobenzylidene)pyrrolidin-2-one (**Py29**).* White solid; yield: 21%; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.31 (s, 1H), 7.65 (dd, J = 7.7, 1.5 Hz, 1H), 7.46–7.48 (m, 2H), 7.39–7.41 (m, 1H), 7.27–7.33 (m, 4H), 6.83 (d, J = 1.4 Hz, 1H), 6.23 (s, 1H), 3.72 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 172.8, 138.6, 136.4, 135.7, 131.8, 131.3, 129.8, 129.6, 128.9, 127.9, 127.9, 108.2, 29.2; HR-MS (ESI): *m/z* calcd for $C_{18}H_{13}C_{l2}NONa$ ([M+Na]$^+$) 352.0266, found 352.0266.

*4.2.3.38. (E)-3-(2-chlorobenzylidene)pyrrolidin-2-one (**Py30**).* Light yellow solid; yield: 35%; mp: 210–212 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.23 (br, 1H), 7.42–7.60 (m, 4H), 7.10 (t, J = 2.8 Hz, 2H), 3.40 (t, J = 6.4 Hz, 2H), 3.10 (td, J = 6.4, 2.7 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.0, 137.8, 134.5, 133.4, 130.4, 128.6, 127.9, 127.7, 126.1, 38.6, 25.6; HR-MS (ESI): *m/z* calcd for $C_{11}H_{10}ClNONa$ ([M+Na]$^+$) 230.0343, found 230.0348.

*4.2.3.39. (E)-3-(4-bromobenzylidene)pyrrolidin-2-one (**Py31**).* White solid; yield: 47%; mp: 236–237 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.18 (br, 1H), 7.47–7.62 (m, 4H), 7.05 (t, J = 2.8 Hz, 1H), 3.36 (t, J = 6.8 Hz, 2H), 3.03 (td, J = 6.7, 2.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.2, 134.8, 133.7, 131.6, 131.1, 126.4, 121.4, 38.6, 25.7; HR-MS (ESI): *m/z* calcd for $C_{11}H_{10}BrNONa$ ([M+Na]$^+$) 273.9838, found 273.9837.

*4.2.3.40. (E)-3-(3-bromobenzylidene)pyrrolidin-2-one (**Py32**).* Light yellow solid; yield: 38%; mp: 247–249 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.20 (br, 1H), 7.37–7.70 (m, 4H), 7.06 (t, J = 2.8 Hz, 1H), 3.36 (t, J = 6.0 Hz, 2H), 3.06 (td, J = 6.0, 2.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.0, 138.1, 134.5, 131.5, 130.8, 130.7, 128.0, 126.1, 122.0, 38.7, 25.6; HR-MS (ESI): *m/z* calcd for $C_{11}H_{10}BrNONa$ ([M+Na]$^+$) 273.9838, found 273.9837.

*4.2.3.41. (E)-3-(2-bromobenzylidene)pyrrolidin-2-one (**Py33**).* Light yellow solid; yield: 35%; mp: 219–221 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.24 (br, 1H), 7.26–7.71 (m, 5H), 3.35 (t, J = 6.2 Hz, 2H), 3.00 (td, J = 6.4, 2.9 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 169.9, 135.5, 134.9, 132.9, 129.9, 129.5, 127.8, 125.8, 124.4, 38.7, 25.3; HR-MS (ESI): *m/z* calcd for $C_{11}H_{10}BrNONa$ ([M+Na]$^+$) 273.9838, found 273.9837.

*4.2.3.42. (E)-3-(2,3-dichlorobenzylidene)pyrrolidin-2-one (**Py34**).* Light yellow solid; yield: 31%; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.31 (br, 1H), 7.41–7.62 (m, 3H), 7.33 (t, J = 3.0 Hz, 1H), 3.35 (t, J = 6.1 Hz, 2H), 3.00 (td, J = 6.4, 2.7 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.1, 137.5, 136.3, 132.8, 131.7, 130.4, 128.7, 128.5, 123.7, 39.2, 25.8; HR-MS (ESI): *m/z* calcd for $C_{11}H_9Cl_2NONa$ ([M+Na]$^+$) 263.9953, found 263.9955.

*4.2.3.43. (E)-3-(3,4-dichlorobenzylidene)pyrrolidin-2-one (**Py35**).* Light yellow solid; yield: 29%; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.22 (br, 1H), 7.50–7.75 (m, 3H), 7.06 (t, J = 2.8 Hz, 1H), 3.37 (t, J = 6.3 Hz, 2H), 3.05 (td, J = 6.3, 2.7 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 170.4, 136.9, 135.7, 131.9, 131.3, 131.2, 131.0, 129.5, 125.7, 39.2, 26.1; HR-MS (ESI): *m/z* calcd for $C_{11}H_9Cl_2NONa$ ([M+Na]$^+$) 263.9953, found 263.9955.

*4.2.3.44. (E)-3-(anthracen-9-ylmethylene)pyrrolidin-2-one (**Py36**).* Light yellow solid; yield: 41%; mp: 254–256 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.62 (br, 1H), 7.52–8.31 (m, 10H), 3.26 (t, J = 6.7 Hz, 2H), 2.32 (td, J = 6.5, 2.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 169.7, 139.1, 131.3, 130.6, 129.3, 128.6, 127.4, 126.7, 125.9, 125.8, 125.3, 38.9, 25.5; HR-MS (ESI): *m/z* calcd for $C_{19}H_{15}NONa$ ([M+Na]$^+$) 296.1046, found 296.1050.

*4.2.3.45. (E)-3-(naphthalen-2-ylmethylene)pyrrolidin-2-one (**Py37**).* Light yellow solid; yield: 39%; mp: 234–236 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 8.15 (br, 1H), 7.52–7.98 (m, 7H), 7.25 (t, J = 2.7 Hz, 1H), 3.41 (t, J = 6.3 Hz, 2H), 3.19 (td, J = 6.5, 2.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 171.0, 133.7, 133.6, 133.5, 132.9, 129.3, 128.7, 128.6, 128.2, 128.0, 127.2, 127.1, 126.9, 39.2, 26.4; HR-MS (ESI): *m/z* calcd for $C_{15}H_{13}NONa$ ([M+Na]$^+$) 246.0889, found 246.0890.

*4.2.3.46. (E)-3-benzylidenepiperidin-2-one (**Pi1**) [65].* White solid; yield: 55%; mp: 156–158 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.78 (br, 1H), 7.55 (t, J = 1.8 Hz, 1H), 7.31–7.42 (m, 4H), 3.22–3.25 (m, 2H), 2.70–2.73 (m, 2H), 1.69–1.74 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 164.9, 136.1, 133.6, 131.4, 130.1, 128.9, 128.4, 41.3, 26.5, 23.2; HR-MS (ESI): *m/z* calcd for $C_{12}H_{13}NONa$ ([M+Na]$^+$) 210.0889, found 210.0892.

*4.2.3.47. (E)-3-(4-methylbenzylidene)piperidin-2-one (**Pi2**) [65].* White solid; yield: 54%; mp: 182–184 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.74 (br, 1H), 7.51 (t, J = 1.9 Hz, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 3.21–3.24 (m, 2H), 2.69–2.74 (m, 2H), 2.31 (s, 3H), 1.68–1.73 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 165.1, 138.0, 133.6, 133.2, 130.5, 130.1, 129.5, 41.3, 26.6, 23.1, 21.3; HR-MS (ESI): *m/z* calcd for $C_{13}H_{15}NONa$ ([M+Na]$^+$) 224.1045, found 224.1050.

*4.2.3.48. (E)-3-(3-methylbenzylidene)piperidin-2-one (**Pi3**) [65].* White solid; yield: 53%; mp: 131–133 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.76 (br, 1H), 7.51 (t, J = 1.9 Hz, 1H), 7.13–7.30 (m, 4H), 3.21–3.24 (m, 2H), 2.69–2.74 (m, 2H), 2.32 (s, 3H), 1.68–1.73 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 165.0, 138.0, 136.0, 133.7, 131.2, 130.6, 129.1, 128.7, 127.2, 41.3, 26.5, 23.3, 21.4; HR-MS (ESI): *m/z* calcd for $C_{13}H_{15}NONa$ ([M+Na]$^+$) 224.1045, found 224.1050.

*4.2.3.49. (E)-3-(2-methylbenzylidene)piperidin-2-one (**Pi4**) [65].* White solid; yield: 51%; mp: 134–136 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.77 (br, 1H), 7.59 (t, J = 1.9 Hz, 1H), 7.19–7.25 (m, 4H), 3.22–3.24 (m, 2H), 2.51–2.54 (m, 2H), 2.22 (s, 3H), 1.65–1.70 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 164.9, 137.1, 135.2, 132.5, 131.8, 130.4, 129.1, 128.3, 125.9, 41.6, 26.2, 23.3, 20.0; HR-MS (ESI): *m/z* calcd for $C_{13}H_{15}NONa$ ([M+Na]$^+$) 224.1045, found 224.1050.

*4.2.3.50. (E)-3-(4-ethylbenzylidene)piperidin-2-one (**Pi5**).* White solid; yield: 59%; mp: 175–176 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.73 (br, 1H), 7.51 (t, J = 1.9 Hz, 1H), 7.33 (d, J = 7.8 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 3.21–3.24 (m, 2H), 2.70–2.73 (m, 2H), 2.60 (q, J = 7.5 Hz, 2H), 1.69–1.73 (m, 2H), 1.18 (t, J = 7.7 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 165.1, 144.3, 133.6, 133.5, 130.6, 130.2, 128.3, 41.3, 28.4, 26.6, 23.3, 12.9; HR-MS (ESI): *m/z* calcd for $C_{14}H_{17}NONa$ ([M+Na]$^+$) 238.1202, found 238.1206.

*4.2.3.51. (E)-3-(4-isopropylbenzylidene)piperidin-2-one (**Pi6**).* White solid; yield: 61%; mp: 186–187 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.74 (br, 1H), 7.52 (t, J = 1.8 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 3.21–3.24 (m, 2H), 2.85–2.92 (m, 1H), 2.70–2.73 (m, 2H), 1.69–1.73 (m, 2H), 1.20 (t, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 165.1, 148.8, 133.6,

133.6, 130.6, 130.2, 126.8, 41.3, 33.7, 26.6, 24.2, 23.3; HR-MS (ESI): *m/z* calcd for $C_{15}H_{19}NONa$ ($[M+Na]^+$) 252.1358, found 252.1362.

4.2.3.52. (E)-3-(4-(tert-butyl)benzylidene)piperidin-2-one (***Pi7***). White solid; yield: 58%; mp: 139–141 °C; ^1H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.74 (br, 1H), 7.52 (t, J = 1.8 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 3.21–3.24 (m, 2H), 2.71–2.73 (m, 2H), 1.69–1.73 (m, 2H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 165.1, 151.0, 133.5, 133.3, 130.7, 129.9, 125.6, 41.3, 34.8, 31.4, 26.6, 23.3; HR-MS (ESI): *m/z* calcd for $C_{16}H_{21}NONa$ ($[M+Na]^+$) 266.1515, found 266.1518.

4.2.3.53. (E)-3-(4-methoxybenzylidene)piperidin-2-one (***Pi8***) [65]. White solid; yield: 54%; mp: 211–213 °C; ^1H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.69 (br, 1H), 7.50 (t, J = 1.9 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 3.78 (s, 3H), 3.21–3.24 (m, 2H), 2.69–2.72 (m, 2H), 1.69–1.74 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 165.2, 159.5, 133.4, 131.8, 129.1, 128.5, 114.4, 55.6, 41.3, 26.6, 23.3; HR-MS (ESI): *m/z* calcd for $C_{13}H_{15}NO_2Na$ ($[M+Na]^+$) 240.0994, found 240.0996.

4.2.3.54. (E)-3-(3-methoxybenzylidene)piperidin-2-one (***Pi9***). White solid; yield: 51%; mp: 192–193 °C; ^1H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.77 (br, 1H), 7.52 (t, J = 1.8 Hz, 1H), 6.89–7.33 (m, 4H), 3.78 (s, 3H), 3.21–3.24 (m, 2H), 2.71–2.74 (m, 2H), 1.68–1.74 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 164.9, 159.6, 137.4, 133.6, 131.6, 129.9, 122.3, 115.4, 114.1, 55.5, 41.3, 26.5, 23.2; HR-MS (ESI): *m/z* calcd for $C_{13}H_{15}NO_2Na$ ($[M+Na]^+$) 240.0994, found 240.0996.

4.2.3.55. (E)-3-(2-methoxybenzylidene)piperidin-2-one (***Pi10***). White solid; yield: 49%; mp: 196–199 °C; ^1H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.72 (br, 1H), 7.65 (t, J = 2.1 Hz, 1H), 6.94–7.33 (m, 4H), 3.80 (s, 3H), 3.22–3.24 (m, 2H), 2.59–2.62 (m, 2H), 1.65–1.70 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 165.1, 157.9, 130.9, 130.2, 130.0, 129.4, 124.6, 114.4, 55.8, 41.5, 26.6, 23.3; HR-MS (ESI): *m/z* calcd for $C_{13}H_{15}NO_2Na$ ($[M+Na]^+$) 240.0994, found 240.0996.

4.2.3.56. (E)-3-(4-ethoxybenzylidene)piperidin-2-one (***Pi11***). White solid; yield: 56%; mp: 225–226 °C; ^1H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.68 (br, 1H), 7.49 (t, J = 1.9 Hz, 1H), 7.37 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 8.5 Hz, 2H), 4.04 (q, J = 7.0 Hz, 2H), 3.21–3.24 (m, 2H), 2.69–2.72 (m, 2H), 1.69–1.74 (m, 2H), 1.33 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 165.2, 158.8, 133.5, 131.8, 129.0, 128.4, 114.8, 63.6, 41.3, 26.6, 23.3; HR-MS (ESI): *m/z* calcd for $C_{14}H_{17}NO_2Na$ ($[M+Na]^+$) 254.1151, found 254.1152.

4.2.3.57. (E)-3-(2-ethoxybenzylidene)piperidin-2-one (***Pi12***). White solid; yield: 47%; mp: 213–216 °C; ^1H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.71 (br, 1H), 7.66 (t, J = 2.1 Hz, 1H), 6.93–7.31 (m, 4H), 4.06 (q, J = 7.0 Hz, 2H), 3.21–3.24 (m, 2H), 2.60–2.63 (m, 2H), 1.66–1.71 (m, 2H), 1.33 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 165.1, 157.1, 130.9, 130.3, 129.6, 124.7, 120.2, 112.4, 63.8, 41.5, 26.6, 23.3; HR-MS (ESI): *m/z* calcd for $C_{14}H_{17}NO_2Na$ ($[M+Na]^+$) 254.1151, found 254.1152.

4.2.3.58. (E)-3-(4-butoxybenzylidene)piperidin-2-one (***Pi13***). White solid; yield: 61%; mp: 257–258 °C; ^1H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.69 (br, 1H), 7.49 (t, J = 1.8 Hz, 1H), 7.36 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 3.98 (t, J = 6.5 Hz, 2H), 3.21–3.24 (m, 2H), 2.69–2.72 (m, 2H), 1.66–1.72 (m, 4H), 1.39–1.46 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 165.2, 159.0, 133.5, 131.8, 129.0, 128.4, 114.8, 67.6, 41.3, 31.1, 26.6, 23.3, 19.2, 14.1; HR-MS (ESI): *m/z* calcd for $C_{16}H_{21}NO_2Na$ ($[M+Na]^+$) 282.1464, found 282.1467.

4.2.3.59. (E)-3-(2-butoxybenzylidene)piperidin-2-one (***Pi14***). White solid; yield: 65%; mp: 236–238 °C; ^1H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.97 (t, J = 2.1 Hz, 1H), 6.92–7.31 (m, 4H), 4.02 (t, J = 6.9 Hz, 2H), 3.44–3.46 (m, 2H), 2.72–2.75 (m, 2H), 1.79–1.89 (m, 4H), 1.48–1.56 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 167.0, 157.4, 131.8, 130.2, 129.5, 129.4, 125.1, 119.7, 111.8, 68.2, 41.2, 31.2, 26.4, 23.1, 19.3, 13.8; HR-MS (ESI): *m/z* calcd for $C_{16}H_{21}NO_2Na$ ($[M+Na]^+$) 282.1464, found 282.1467.

4.2.3.60. (E)-3-(2-(isopentyloxy)benzylidene)piperidin-2-one (***Pi15***). White solid; yield: 53%; mp: 269–271 °C; ^1H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.97 (t, J = 2.1 Hz, 1H), 6.93–7.31 (m, 4H), 4.05 (t, J = 6.9 Hz, 2H), 3.44–3.46 (m, 2H), 2.72–2.75 (m, 2H), 1.83–1.91 (m, 3H), 1.72–1.76 (m, 2H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 166.9, 157.4, 131.8, 130.2, 129.5, 129.4, 125.1, 119.7, 111.7, 66.9, 42.2, 37.9, 26.4, 25.1, 23.1, 22.6; HR-MS (ESI): *m/z* calcd for $C_{17}H_{23}NO_2Na$ ($[M+Na]^+$) 296.1621, found 296.1623.

4.2.3.61. (E)-3-(2-(dodecyloxy)benzylidene)piperidin-2-one (***Pi16***). White solid; yield: 58%; ^1H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.97 (t, J = 2.1 Hz, 1H), 6.92–7.31 (m, 4H), 6.83 (br, 1H), 4.01 (t, J = 6.9 Hz, 2H), 3.44–3.46 (m, 2H), 2.72–2.75 (m, 2H), 1.80–1.89 (m, 4H), 1.44–1.50 (m, 2H), 1.30–1.36 (m, 16H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 166.9, 157.4, 131.8, 130.2, 129.5, 129.4, 125.1, 119.7, 111.8, 68.5, 42.2, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 26.4, 26.0, 23.1, 22.7, 14.1; HR-MS (ESI): *m/z* calcd for $C_{24}H_{37}NO_2Na$ ($[M+Na]^+$) 394.2717, found 394.2723.

4.2.3.62. (E)-3-(2-(benzyloxy)benzylidene)piperidin-2-one (***Pi17***). White solid; yield: 51%; mp: 259–262 °C; ^1H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.06 (t, J = 1.7 Hz, 1H), 6.97–7.47 (m, 9H), 6.77 (br, 1H), 5.17 (s, 2H), 3.42–3.45 (m, 2H), 2.73–2.76 (m, 2H), 1.83–1.88 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 166.8, 156.9, 137.0, 131.6, 130.6, 129.9, 129.4, 128.5, 127.7, 127.0, 125.5, 120.3, 112.6, 70.3, 42.2, 26.4, 23.0; HR-MS (ESI): *m/z* calcd for $C_{19}H_{19}NO_2Na$ ($[M+Na]^+$) 316.1307, found 316.1313.

*4.2.3.63. (E)-3-(2-((tert-butyldimethylsilyl)oxy)benzylidene)piperidin-2-one (**18**).* White solid; yield: 50%; ^1H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.78 (t, J = 1.7 Hz, 1H), 6.82–7.30 (m, 4H), 3.45–3.47 (m, 2H), 2.82–2.85 (m, 2H), 1.89–1.91 (m, 4H), 1.02 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 167.0, 155.5, 137.1, 135.6, 129.2, 122.8, 121.3, 120.0, 42.0, 26.2, 25.6, 23.0, 18.2, −4.3; ESI-MS: *m/z* 304.5 ($[M+H^+]$).

4.2.3.64. (E)-3-(2-hydroxybenzylidene)piperidin-2-one (***Pi19***). White solid; yield: 34%; ^1H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 9.47 (s, 1H), 7.76 (s, 1H), 6.72–7.45 (m, 4H), 3.21–3.24 (m, 2H), 2.68–2.71 (m, 2H), 1.69–1.73 (m, 4H),; ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 165.0, 157.7, 137.2, 133.8, 131.1, 129.8, 121.0, 116.6, 115.6, 41.3, 26.6, 23.2; HR-MS (ESI): *m/z* calcd for $C_{12}H_{13}NO_2Na$ ($[M+Na]^+$) 226.0838, found 226.0839.

4.2.3.65. (E)-3-(4-fluorobenzylidene)piperidin-2-one (***Pi20***) [65]. White solid; yield: 65%; mp: 189–190 °C; ^1H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.77 (br, 1H), 7.53 (s, 1H), 7.22–7.49 (m, 4H), 3.22–3.24 (m, 2H), 2.68–2.71 (m, 2H), 1.69–1.74 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 164.9, 162.0, 132.5, 132.3, 132.2, 131.3, 115.9, 115.7, 41.3, 26.4, 23.2; HR-MS (ESI): *m/z* calcd for $C_{12}H_{12}FNONa$ ($[M+Na]^+$) 228.0795, found 228.0799.

4.2.3.66. (E)-3-(2-fluorobenzylidene)piperidin-2-one (***Pi21***). White solid; yield: 57%; mp: 162–164 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.86 (br, 1H), 7.22–7.55 (m, 5H), 3.23–3.25 (m, 2H), 2.59–2.62 (m, 2H), 1.68–1.74 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 164.4, 160.0, 133.8, 131.0, 130.6, 125.9, 124.7, 123.6, 116.0, 41.5, 26.5, 23.1; HR-MS (ESI): *m/z* calcd for $C_{12}H_{12}FNONa$ ([M+Na]$^+$) 228.0795, found 228.0799.

4.2.3.67. (E)-3-(4-(trifluoromethyl)benzylidene)piperidin-2-one (***Pi22***) [65]. White solid; yield: 59%; mp: 168–170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.83 (s, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.24 (br, 1H), 3.46–3.49 (m, 2H), 2.79–2.82 (m, 2H), 1.88–1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 166.3, 139.4, 133.9, 131.7, 129.8, 129.7, 125.2, 124.1, 42.0, 26.2, 22.9; HR-MS (ESI): *m/z* calcd for $C_{13}H_{12}F_3NONa$ ([M+Na]$^+$) 278.0763, found 278.0767.

4.2.3.68. (E)-3-(2-(trifluoromethyl)benzylidene)piperidin-2-one (***Pi23***). White solid; yield: 45%; mp: 154–156 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.92 (s, 1H), 7.26–7.70 (m, 4H), 7.13 (br, s), 3.41–3.44 (m, 2H), 2.48–2.51 (m, 2H), 1.79–1.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 166.1, 135.0, 132.5, 132.5, 131.4, 130.4, 128.7, 127.7, 125.9, 139.8, 42.2, 25.9, 22.8; HR-MS (ESI): *m/z* calcd for $C_{13}H_{12}F_3NONa$ ([M+Na]$^+$) 278.0763, found 278.0767.

4.2.3.69. (E)-3-(4-chlorobenzylidene)piperidin-2-one (***Pi24***) [65]. White solid; yield: 65%; mp: 145–146 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.81 (br, 1H), 7.51 (t, J = 1.9 Hz, 1H), 7.43–7.47 (m, 4H), 3.22–3.24 (m, 2H), 2.68–2.71 (m, 2H), 1.69–1.74 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 164.7, 134.9, 133.0, 132.3, 132.2, 131.8, 128.9, 41.3, 26.4, 23.2; HR-MS (ESI): *m/z* calcd for $C_{12}H_{12}ClNONa$ ([M+Na]$^+$) 244.0499, found 244.0507.

4.2.3.70. (E)-3-(3-chlorobenzylidene)piperidin-2-one (***Pi25***) [65]. White solid; yield: 59%; mp: 178–179 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.83 (br, 1H), 7.51 (t, J = 1.9 Hz, 1H), 7.36–7.45 (m, 4H), 3.22–3.24 (m, 2H), 2.68–2.71 (m, 2H), 1.69–1.74 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 164.6, 138.3, 133.6, 133.0, 132.1, 130.7, 129.5, 128.6, 128.2, 41.3, 26.4, 23.1; HR-MS (ESI): *m/z* calcd for $C_{12}H_{12}ClNONa$ ([M+Na]$^+$) 244.0499, found 244.0507.

4.2.3.71. (E)-3-(2-chlorobenzylidene)piperidin-2-one (***Pi26***). White solid; yield: 52%; mp: 138–139 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.86 (br, 1H), 7.61 (t, J = 1.9 Hz, 1H), 7.36–7.53 (m, 4H), 3.23–3.25 (m, 2H), 2.56–2.59 (m, 2H), 1.68–1.72 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 164.4, 134.2, 133.7, 133.5, 131.1, 130.2, 130.1, 129.9, 127.4, 41.5, 26.2, 23.1; HR-MS (ESI): *m/z* calcd for $C_{12}H_{12}ClNONa$ ([M+Na]$^+$) 244.0499, found 244.0507.

4.2.3.72. (E)-3-(4-bromobenzylidene)piperidin-2-one (***Pi27***) [65]. White solid; yield: 55%; mp: 169–171 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.81 (br, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.49 (s, 1H), 7.36 (d, J = 8.5 Hz, 2H), 3.21–3.24 (m, 2H), 2.66–2.69 (m, 2H), 1.68–1.73 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 164.7, 135.3, 132.4, 132.2, 132.1, 131.8, 41.3, 26.4, 23.2; HR-MS (ESI): *m/z* calcd for $C_{12}H_{12}BrNONa$ ([M+Na]$^+$) 287.9994, found 287.9996.

4.2.3.73. (E)-3-(3-bromobenzylidene)piperidin-2-one (***Pi28***). White solid; yield: 45%; mp: 152–153 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.83 (br, 1H), 7.35–7.58 (m, 5H), 3.21–3.24 (m, 2H), 2.68–2.71 (m, 2H), 1.69–1.74 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 164.6, 138.5, 133.0, 132.3, 132.0, 131.1, 130.9, 129.0, 122.2, 41.3, 26.4, 23.1; HR-MS (ESI): *m/z* calcd for $C_{12}H_{12}BrNONa$ ([M+Na]$^+$) 287.9994, found 287.9996.

4.2.3.74. (E)-3-(2-bromobenzylidene)piperidin-2-one (***Pi29***). White solid; yield: 48%; mp: 139–141 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 7.86 (br, 1H), 7.25–7.69 (m, 5H), 3.22–3.25 (m, 2H), 2.54–2.56 (m, 2H), 1.67–1.72 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 164.4, 136.0, 133.1, 133.1, 132.6, 131.1, 130.3, 127.9, 124.4, 41.5, 26.1, 23.1; HR-MS (ESI): *m/z* calcd for $C_{12}H_{12}BrNONa$ ([M+Na]$^+$) 287.9994, found 287.9996.

4.2.3.75. (E)-3-(2,4-dichlorobenzylidene)piperidin-2-one (***Pi30***). White solid; yield: 41%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.79 (s, 1H), 7.68 (br, 1H), 7.20–7.44 (m, 3H), 3.43–3.46 (m, 2H), 2.60–2.62 (m, 2H), 1.83–1.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 166.3, 135.2, 134.3, 132.9, 132.3, 131.3, 131.0, 129.5, 126.6, 42.0, 26.1, 22.8; HR-MS (ESI): *m/z* calcd for $C_{12}H_{11}Cl_2NONa$ ([M+Na]$^+$) 278.0109, found 278.0114.

4.2.3.76. (E)-3-(2,3-dichlorobenzylidene)piperidin-2-one (***Pi31***). White solid; yield: 39%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.84 (s, 1H), 7.16–7.45 (m, 4H), 3.45–3.48 (m, 2H), 2.60–2.63 (m, 2H), 1.84–1.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 166.1, 136.7, 133.4, 132.5, 132.4, 132.3, 129.8, 128.4, 126.8, 42.1, 26.0, 22.8; HR-MS (ESI): *m/z* calcd for $C_{12}H_{11}Cl_2NONa$ ([M+Na]$^+$) 278.0109, found 278.0114.

4.2.3.77. (E)-3-(3,4-dichlorobenzylidene)piperidin-2-one (***Pi32***) [65]. White solid; yield: 41%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.77 (s, 1H), 7.21–7.48 (m, 3H), 7.14 (br, 1H), 3.45–3.48 (m, 2H), 2.77–2.80 (m, 2H), 1.88–1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 166.2, 135.8, 133.0, 132.5, 132.1, 131.3, 131.2, 130.6, 129.0, 41.9, 26.2, 22.9; HR-MS (ESI): *m/z* calcd for $C_{12}H_{11}Cl_2NONa$ ([M+Na]$^+$) 278.0109, found 278.0114.

4.2.4. General procedure for synthesis of compounds ***9a-d***. [46,53]

4.2.4.1. 5-Substituted isatin (***8a-d***). To a solution of choral hydrate in water were added sodium sulfate (6.0 eq) and appropriate aniline (1.0 eq) followed by a solution of hydroxylamine hydrochloride solution (3.0 eq) in water. The reaction mixture was heated at 55 °C with stirring overnight and then cooled to room temperature. The resulting precipitate was filtered and dried to obtain the isonitrosoacetanilide intermediates. The isonitrosoacetanilide was added to a stirring solution of concentrated sulfuric acid slowly to keep the temperature in the range of 60–70 °C. Upon completion of the addition, the mixture was heated to 90 °C for 10 min and then poured into crushed ice and stirred for 30 min. The precipitate was filtered and washed three times with water and dried under vacuum to afford the solids **8a-d**.

4.2.4.2. 5-Fluoroisatin (***8a***) [66]. Orange red powder; mp: 221–223 °C; yield: 48%; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 11.02 (s, 1H), 7.41 (m, 1H), 7.32 (dd, J = 7.2, 2.7 Hz, 1H), 6.91 (dd, J = 8.5, 4.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 184.4, 159.9, 158.6, 147.4, 124.9, 118.9, 113.9, 111.8; ESI-MS: *m/z* 166.0 ([M+H]$^+$).

4.2.4.3. 5-Chloroisatin (***8b***) [66]. Orange red powder; mp: 245–247 °C; yield: 53%; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 11.15 (s, 1H), 7.60 (dd, J = 8.3, 1.3 Hz, 1H), 7.54 (d, J = 1.3 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 183.8, 159.6, 149.7, 137.7, 127.3, 124.6, 119.6, 114.3; ESI-MS: *m/z* 184.0 ([M+H]$^+$).

4.2.4.4. 5-bromoisatin (***8c***) [66]. Red powder; mp: 251–254 °C; yield: 41%; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 11.11 (s, 1H), 7.74 (dd, J = 8.3, 1.3 Hz, 1H), 7.63 (d, J = 1.3 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 183.6,

159.4, 150.0, 140.5, 127.3, 126.4, 120.0, 114.7; ESI-MS: *m/z* 227.9 ($[M+H]^+$).

*4.2.4.5. 5-Methylisatin (**8d**) [66].* Red powder; mp: 187–189 °C; yield: 46%; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.93 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 6.76 (d, J = 8.0 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 185.0, 159.9, 149.0, 139.2, 132.4, 125.2, 118.2, 112.5; ESI-MS: *m/z* 162.0 ($[M+H]^+$).

*4.2.4.6. 5-Substituted oxindole (**9a-d**).* $TiCl_4$ (0.7 mL, 6 mmol) was added to a stirred suspension of Zn powder (0.78 g, 12 mmol) in freshly distilled anhydrous THF (15 mL) at room temperature (r.t.) under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to r.t. A solution of isatin derivatives (2 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at room temperature for about 5 min under N_2. After this period, the thin layer chromatography (TLC) analysis of the mixture showed the reaction completed. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with water (3 50 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (petroleum ether/EtOAc = 5:1) to give the pure products **9a**-**d**.

*4.2.4.7. 5-Fluorooxindole (**9a**) [67].* Light purple solid; mp: 143–144 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.31 (br, 1H), 6.75–7.09 (m, 3H), 3.48 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 176.6, 158.0, 140.3, 128.1, 114.0, 112.6, 110.0, 36.6; ESI-MS: *m/z* 152.0 ($[M+H]^+$).

*4.2.4.8. 5-Chlorooxindole (**9b**) [67].* White solid; mp: 193–195 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.46 (br, 1H), 6.78–7.25 (m, 3H), 3.49 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 176.5, 143.3, 128.5, 127.7, 125.5, 124.9, 110.7, 36.3; ESI-MS: *m/z* 168.0 ($[M+H]^+$).

*4.2.4.9. 5-bromooxindole (**9c**) [68].* White solid; mp: 215–217 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.49 (br, 1H), 6.77–7.40 (m, 3H), 3.52 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 176.3, 143.5, 130.5, 129.0, 127.7, 113.2, 111.3, 36.2; ESI-MS: *m/z* 212.0 ($[M+H]^+$).

*4.2.4.10. 5-Methyloxindole (**9d**) [67].* White solid; mp: 172–174 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.23 (br, 1H), 6.67–7.00 (m, 3H), 3.40 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 176.7, 141.6, 130.3, 128.0, 126.3, 125.5, 109.2, 36.2, 21.1; ESI-MS: *m/z* 148.0 ($[M+H]^+$).

*4.2.5. General procedure for synthesis of 3-benzylideneindolin-2-ones **Ox1-33**. [45]*

The appropriate aldehyde (1 equiv) was added to EtOH (3 mL/0.2 mmol) and the mixture was stirred until complete solution. The oxindole (1 equiv) and piperidine (0.1 equiv) were added, and the mixture was heated to 90°C for 3–7 h, and cooled. The resulting precipitate was filtered, washed with cold ethanol and dried to give the pure compound. If necessary, additional recrystallization in ethanol was applied to obtain the pure product.

*4.2.5.1. (E)-3-benzylideneindolin-2-one (**Ox1**) [48].* Yellow solid; yield 58%, mp 179–180 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.25 (br, 1H), 7.89 (s, 1H), 7.71 (d, J = 7.1 Hz, 2H), 7.68 (d, J = 7.6 Hz, 1H), 7.45–7.53 (m, 3H), 7.27 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.91 (t, J = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.6, 141.8, 137.5, 134.8, 129.9, 129.7, 129.3, 128.7, 127.7, 123.0, 121.8, 121.7, 110.3; ESI-MS: *m/z* 222.2 ($[M+H]^+$).

*4.2.5.2. (E)-3-(4-methylbenzylidene)indolin-2-one (**Ox2**) [48].* Yellow solid; yield 86%, mp 199–200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.89 (br, 1H), 7.82 (s, 1H), 7.71 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.19–7.29 (m, 3H), 6.85–6.93 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.5, 141.5, 140.1, 137.8, 131.9, 129.6, 129.5, 129.3, 126.8, 122.9, 121.8, 121.7, 110.2, 21.6; ESI-MS: *m/z* 236.2 ($[M+H]^+$).

*4.2.5.3. (E)-3-(3-methylbenzylidene)indolin-2-one (**Ox3**) [48].* Yellow solid; yield 86%, mp 138–139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.68 (br, 1H), 7.83 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 7.20–7.27 (m, 3H), 6.86–6.93 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.2, 138.3, 137.8, 134.7, 130.4, 129.9, 129.7, 128.5, 126.3, 123.0, 121.7, 110.1, 21.3; ESI-MS: *m/z* 236.2 ($[M+H]^+$).

*4.2.5.4. (E)-3-(2-methylbenzylidene)indolin-2-one (**Ox4**) [48].* Yellow solid; yield 72%, mp 133–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.45 (br, 1H), 7.91 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.18–7.37 (m, 4H), 6.79–6.91 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 169.7, 137.3, 136.9, 130.4, 129.7, 129.4, 128.4, 125.7, 123.1, 121.8, 109.9, 19.9; ESI-MS: *m/z* 236.2 ($[M+H]^+$).

*4.2.5.5. (E)-3-(4-ethylbenzylidene)indolin-2-one (**Ox5**) [48].* Yellow solid; yield 65%, mp 165–167 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.56 (br, 1H), 7.86 (s, 1H), 7.61–7.78 (m, 3H), 7.35 (d, J = 7.5 Hz, 2H), 7.21 (t, J = 7.7 Hz, 1H), 6.85 (t, J = 8.3 Hz, 2H), 2.67 (q, J = 7.5 Hz, 2H), 1.21 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.3, 146.4, 141.3137.8, 132.0, 129.6, 129.5, 128.1, 126.6, 122.9, 121.8, 121.7, 110.0, 28.8, 15.3; ESI-MS: *m/z* 250.3 ($[M+H]^+$).

*4.2.5.6. (E)-3-(4-isopropylbenzylidene)indolin-2-one (**Ox6**) [69].* Yellow solid; yield 635%, mp 171–173 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.33 (br, 1H), 7.88 (s, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.5 Hz, 1H), 7.38 (t, J = 7.8 Hz, 2H), 7.26 (t, J = 7.7 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 6.94 (t, J = 7.7 Hz, 1H), 2.99–3.00 (m, 1H), 1.35 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.9, 151.1, 141.7, 137.8, 132.3, 129.7, 129.7, 126.8, 126.7, 123.0, 121.9, 121.7, 110.3, 34.2, 23.8; ESI-MS: *m/z* 264.3 ($[M+H]^+$).

*4.2.5.7. (E)-3-(4-(tert-butyl)benzylidene)indolin-2-one (**Ox7**).* Yellow solid; yield 57%, mp 161–163 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.52 (br, 1H), 7.89 (s, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.5 Hz, 1H), 7.26 (t, J = 7.8 Hz, 2H), 7.00 (d, J = 7.8 Hz, 1H), 6.94 (t, J = 7.8 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 171.0, 153.3, 141.8, 137.7, 131.9, 129.7, 129.5, 126.9, 125.6, 123.0, 121.9, 121.7, 110.4, 35.0, 31.2; ESI-MS: *m/z* 278.4 ($[M+H]^+$).

*4.2.5.8. (E)-3-(4-methoxybenzylidene)indolin-2-one (**Ox8**) [48].* Yellow solid; yield 75%, mp 158–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.85 (br, 1H), 7.79 (s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.20 (t, J = 7.8 Hz, 2H), 6.99 (d, J = 7.8 Hz, 1H), 6.87–6.93 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.8, 161.0, 141.4, 137.8, 131.6, 129.5, 127.2, 125.7, 122.7, 122.1, 121.8, 114.2, 110.3, 55.5; ESI-MS: *m/z* 252.4 ($[M+H]^+$).

*4.2.5.9. (E)-3-(3-methoxybenzylidene)indolin-2-one (**Ox9**) [48].* Yellow solid; yield 68%, mp 151–152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.39 (br, 1H), 7.81 (s, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.39 (t, J = 7.4 Hz, 1H), 7.16–7.26 (m, 4H), 6.98 (dd, J = 6.8, 2.4 Hz, 1H),

6.87–6.90 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.0, 159.7, 137.4, 129.9, 129.8, 123.3, 121.9, 121.7, 115.7, 114.2, 55.4; ESI-MS: *m/z* 252.4 ($[M+H]^+$).

*4.2.5.10. (E)-3-(2-methoxybenzylidene)indolin-2-one (**Ox10**) [48].* Yellow solid; yield 71%, mp 221–223 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.58 (br, 1H), 7.66–7.67 (m, 2H), 7.47 (td, J = 7.5, 1.0 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.20 (td, J = 7.8, 0.9 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.82 (t, J = 7.7 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 169.0, 158.1, 143.2, 132.2, 132.2, 130.3, 129.9, 127.8, 123.3, 122.7, 121.5, 121.5, 120.7, 112.0, 110.5, 56.0; ESI-MS: *m/z* 252.4 ($[M+H]^+$).

*4.2.5.11. (E)-3-(4-ethoxybenzylidene)indolin-2-one (**Ox11**) [70].* Yellow solid; yield 56%, mp 169–171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.88 (br, 1H), 7.84 (s, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.69 (d, J = 7.8 Hz, 2H), 7.23 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 6.91–6.96 (m, 2H), 4.12 (q, J = 6.8 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.6, 160.4, 141.5, 137.7, 131.5, 129.3, 127.1, 125.7, 122.7, 122.1, 121.6, 114.6, 110.1, 63.7, 14.7; ESI-MS: *m/z* 266.3 ($[M+H]^+$).

*4.2.5.12. (E)-3-(2-ethoxybenzylidene)indolin-2-one (**Ox12**).* Yellow solid; yield 68%, mp 199–202 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.70 (br, 1H), 8.07 (s, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.44 (td, J = 7.8, 1.2 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.88 (t, J = 7.8 Hz, 1H), 4.15 (q, J = 6.8 Hz, 2H), 1.45 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.9, 157.6, 141.7, 134.3, 131.5, 130.1, 129.5, 127.4, 123.9, 122.9, 122.1, 121.5, 120.0, 111.9, 110.3, 64.0, 14.8; ESI-MS: *m/z* 266.3 ($[M+H]^+$).

*4.2.5.13. 3-(4-(Trifluoromethyl)benzylidene)indolin-2-one (**Ox13**) [48].* Yellow solid; yield 51%, ratio of diastereoisomers E/Z = 57/43; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.21 (br, 1H + 1H, major + minor), 8.31 (d, J = 8.3 Hz, 2H, minor), 7.80 (s, 1H, minor), 7.68–7.75 (m, 4H, major), 7.54 (d, J = 7.5 Hz, 2H, minor), 7.48 (t, J = 7.9 Hz, 1H, major), 7.23–7.29 (m, 1H + 1H, major + minor), 7.07 (t, J = 7.7 Hz, 1H, major), 6.90 (dd, J = 16.2, 7.9 Hz, 2H, major), 6.87 (d, J = 7.5 Hz, 1H, minor); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.37, 143.35, 138.82, 133.69, 130.76, 129.93, 129.60, 129.42, 129.18, 125.88, 125.67, 125.63, 122.65, 122.28, 121.34, 120.47, 110.36; ESI-MS: *m/z* 290.2 ($[M+H]^+$).

*4.2.5.14. (E)-3-(2-(trifluoromethyl)benzylidene)indolin-2-one (**Ox14**) [48].* Yellow solid; yield 32%, mp 175–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.26 (br, 1H), 8.01 (s, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 6.99 (dd, J = 14.5, 7.7 Hz, 2H), 6.81 (t, J = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 169.7, 142.1, 133.7, 133.1, 131.9, 130.4, 130.2, 129.2, 129.0, 126.4, 123.8, 123.2, 121.9, 121.2, 110.5; ESI-MS: *m/z* 290.2 ($[M+H]^+$).

*4.2.5.15. (E)-3-(4-fluorobenzylidene)indolin-2-one (**Ox15**) [48].* Yellow solid; yield 85%, mp 186–189 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.16 (br, 1H), 7.82 (s, 1H), 7.69–7.71 (m, 2H), 7.62 (d, J = 7.7 Hz, 1H), 7.19–7.21 (m, 3H), 6.98 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.4, 162.3, 141.8, 136.2, 131.4, 130.9, 130.0, 127.6, 122.8, 121.9, 121.5, 115.8, 110.4; ESI-MS: *m/z* 240.2 ($[M+H]^+$).

*4.2.5.16. (E)-3-(2-fluorobenzylidene)indolin-2-one (**Ox16**) [48].* Yellow solid; yield 81%, mp 218–220 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.18 (br, 1H), 7.77 (s, 1H), 7.68 (t, J = 7.4 Hz, 1H), 7.37–7.42 (m, 2H), 7.15–7.23 (m, 3H), 6.82–6.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 169.8, 160.0, 142.2, 131.4, 130.2, 130.1, 129.6, 129.4, 124.0, 123.0, 122.8, 121.8, 121.5, 116.0, 110.2; ESI-MS: *m/z* 240.2 ($[M+H]^+$).

*4.2.5.17. (E)-3-(4-chlorobenzylidene)indolin-2-one (**Ox17**) [48].* Yellow solid; yield 71%, mp 189–191 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.97 (br, 1H), 7.79 (s, 1H), 7.58–7.64 (m, 3H), 7.48 (d, J = 8.5 Hz, 2H), 7.25 (t, J = 7.6 Hz, 1H), 6.89–6.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.1, 135.7, 135.5, 133.4, 130.6, 130.1, 129.0, 128.2, 123.0, 121.9, 121.5, 110.4; ESI-MS: *m/z* 256.3 ($[M+H]^+$).

*4.2.5.18. (E)-3-(3-chlorobenzylidene)indolin-2-one (**Ox18**) [48].* Yellow solid; yield 68%, mp 169–170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.52 (br, 1H), 7.77 (s, 1H), 7.66 (s, 1H), 7.55–7.58 (m, 2H), 7.43–7.44 (m, 2H), 7.25 (t, J = 7.7 Hz, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.4, 142.1, 136.7, 135.4, 134.7, 130.4, 130.0, 129.5, 129.0, 128.9, 127.3, 123.1, 122.0, 121.2, 110.6; ESI-MS: *m/z* 256.3 ($[M+H]^+$).

*4.2.5.19. (E)-3-(2-chlorobenzylidene)indolin-2-one (**Ox19**) [48].* Yellow solid; yield 65%, mp 225–227 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.35 (br, 1H), 7.92 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.55 (m, J = 7.5 Hz, 1H), 7.36–7.44 (m, 3H), 7.26 (t, J = 7.7 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 6.86 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.1, 142.0, 134.5, 133.8, 133.5, 130.7, 130.3, 130.2, 130.0, 129.2, 126.6, 123.2, 121.9, 121.3, 110.5; ESI-MS: *m/z* 256.3 ($[M+H]^+$).

*4.2.5.20. (E)-3-(4-bromobenzylidene)indolin-2-one (**Ox20**) [71].* Yellow solid; yield 55%, mp 195–196 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.66 (br, 1H), 7.76 (s, 1H), 7.55–7.64 (m, 5H), 7.26 (t, J = 7.7 Hz, 1H), 6.89–6.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 169.9, 141.8, 135.7, 133.8, 131.9, 130.8, 130.1, 128.2, 123.8, 123.0, 121.9, 121.5, 110.3; ESI-MS: *m/z* 300.1 ($[M+H]^+$).

*4.2.5.21. (E)-3-(3-bromobenzylidene)indolin-2-one (**Ox21**) [72].* Yellow solid; yield 64%, mp 175–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.32 (br, 1H), 7.79 (s, 1H), 7.73 (s, 1H), 7.53–7.58 (m, 3H), 7.35 (t, J = 7.4 Hz, 1H), 7.22–7.24 (m, 1H), 6.86–6.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 169.6, 141.7, 137.0, 135.3, 132.4, 131.9, 130.4, 130.2, 128.6, 127.7, 123.2, 122.8, 122.1, 121.3, 110.3; ESI-MS: *m/z* 300.1 ($[M+H]^+$).

*4.2.5.22. (E)-3-(2-bromobenzylidene)indolin-2-one (**Ox22**) [73].* Yellow solid; yield 62%, mp 204–206 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.24 (br, 1H), 7.80 (s, 1H), 7.69–7.72 (m, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.20–7.33 (m, 4H), 6.89 (d, J = 7.9 Hz, 1H), 6.80–6.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 169.3, 141.6, 135.8, 135.5, 133.2, 130.8, 130.2, 128.7, 127.2, 124.2, 123.3, 121.9, 121.4, 110.2; ESI-MS: *m/z* 300.1 ($[M+H]^+$).

*4.2.5.23. (Z)-3-(2,4-dichlorobenzylidene)indolin-2-one (**Ox23**) [70].* Yellow solid; yield 39%, mp 215–216 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.62 (br, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.70–7.76 (m, 3H), 7.46 (t, J = 7.5 Hz, 1H), 7.24–7.28 (m, 1H), 6.97–7.01 (m, 1H), 6.83 (d, J = 6.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 166.9, 142.0, 134.9, 134.6, 133.9, 131.5, 130.5, 129.8, 128.9, 127.0, 123.9, 121.8, 121.1, 110.1; ESI-MS: *m/z* 290.3 ($[M+H]^+$).

*4.2.5.24. (E)-3-(2,3-dichlorobenzylidene)indolin-2-one (**Ox24**) [48].* Yellow solid; yield 48%, mp 218–220 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.69 (br, 1H), 7.70–7.79 (m, 2H), 7.48–7.54 (m, 2H),7.21–7.24 (m, 1H), 7.05 (d, J = 7.0 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 6.77–6.81 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 167.8, 143.1, 135.3, 131.2, 130.8, 130.7, 130.5, 129.9, 128.8, 128.4, 122.6, 121.1,

120.1, 110.2; ESI-MS: *m/z* 290.3 ($[M+H]^+$).

*4.2.5.25. (Z)-3-(anthracen-9-ylmethylene)indolin-2-one (**Ox25**).* Yellow solid; yield 67%, mp 197–199 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 8.44 (br, 1H), 8.17 (s, 1H), 8.01 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.88–7.91 (m, 2H), 7.78 (dd, J = 7.6, 2.0 Hz, 1H), 7.69 (d, J = 6.8 Hz, 1H), 7.56–7.59 (m, 2H), 7.24 (td, J = 7.6, 2.0 Hz, 1H), 6.85–6.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 170.0, 141.5, 137.5, 133.7, 132.2, 129.9, 129.3, 128.4, 128.3, 127.8, 127.2, 126.7, 126.3, 123.0, 121.8, 121.8, 110.1; ESI-MS: *m/z* 322.3 ($[M+H]^+$).

*4.2.5.26. (E)-3-(4-hydroxybenzylidene)indolin-2-one (**Ox26**) [48].* Yellow solid; yield 59%, mp 254–256 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.53 (br, 1H), 10.17 (br, 1H), 7.76 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.29 (t, J = 7.3 Hz, 1H), 7.19 (t, J = 7.2 Hz, 1H), 6.81–6.97 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 169.2, 156.9, 143.0, 132.9, 132.0, 130.1, 130.0, 126.9, 122.7, 121.8, 121.4, 119.2, 116.4, 110.4; ESI-MS: *m/z* 238.3 ($[M+H]^+$).

*4.2.5.27. (E)-3-(3-hydroxybenzylidene)indolin-2-one (**Ox27**) [48].* Yellow solid; yield 56%, mp 268–270 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.55 (s, 1H), 9.70 (s, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.52 (s, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 6.94 (m, 2H), 6.85 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 169.0, 157.9, 143.3, 136.4, 136.0, 130.4, 130.3, 127.8, 123.0, 121.5, 121.2, 120.5, 117.2, 115.9, 117.2, 115.9, 110.4; ESI-MS: *m/z* 238.3 ($[M+H]^+$).

*4.2.5.28. (Z)-3-(2-hydroxybenzylidene)indolin-2-one (**Ox28**) [48].* Yellow solid; yield 64%, mp 204–205 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.46 (s, 1H), 10.06 (s, 1H), 7.69 (d, J = 7.52 Hz, 1H), 7.62 (d, J = 8.54 Hz, 2H), 7.54 (s, 1H), 7.21 (td, J = 7.52, 1.09 Hz, 1H), 6.86–6.93 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 169.5, 159.9, 143.0, 140.4, 137.0, 135.2, 132.2, 129.8, 128.2, 125.2, 121.4, 116.1, 110.4; ESI-MS: *m/z* 238.3 ($[M+H]^+$).

*4.2.5.29. 3-(3-Chlorobenzylidene)-5-fluoroindolin-2-one (**Ox29**).* Yellow solid; yield 56%; ratio of diastereoisomers E/Z = 53/47; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.67 (br, 1H, major), 10.65 (br, 1H, minor), 8.64 (s, 1H, minor), 8.16 (d, J = 6.6 Hz, 1H, minor), 7.86 (s, 1H, minor), 7.73 (s, 1H, major), 7.64–7.66 (m, 1H + 1H, major + minor), 7.61–7.63 (m, 1H, major), 7.56–7.57 (m, 2H, major), 7.50–7.51 (m, 2H, minor), 7.03–7.21 (m, 2H + 1H, major + minor), 6.85–6.88 (m, 1H, major), 6.79–6.82 (m, 1H, minor); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 168.7, 167.4, 158.9, 157.0, 140.0, 137.7, 136.9, 136.7, 136.4, 134.0, 133.4, 131.4, 131.2, 130.7, 130.5, 131.1, 129.3, 129.0, 128.3, 128.0, 126.5, 122.0, 117.3, 116.1, 111.5, 110.7, 110.0, 108.0; ESI-MS: *m/z* 274.2 ($[M+H]^+$).

*4.2.5.30. 5-Chloro-3-(3-chlorobenzylidene)indolin-2-one (**Ox30**).* Yellow solid; yield 68%; ratio of diastereoisomers E/Z = 35/65; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.82 (br, 1H, major), 10.80 (br, 1H, minor), 8.67 (s, 1H, major), 8.20 (d, J = 5.9 Hz, major), 7.95 (s, 1H, major), 7.84–7.86 (m, 2H, minor), 7.76–7.77 (m, 1H, minor), 7.69–7.70 (m, 1H, major), 7.52–7.60 (m, 1H + 2H, major + minor), 7.28–7.33 (m, 1H + 2H, major + minor), 6.91–6.93 (m, 1H, minor), 6.85–6.87 (m, 1H, major); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 168.4, 167.2, 142.4, 140.2, 137.2, 136.7, 136.3, 136.1, 134.0, 133.4, 131.4, 131.3, 131.2, 130.5, 130.4, 130.1, 129.3, 128.5, 128.1, 127.6, 126.9, 126.0, 125.4, 122.7, 122.4, 120.6, 112.1, 113.3; ESI-MS: *m/z* 290.2 ($[M+H]^+$).

*4.2.5.31. 5-Bromo-3-(3-chlorobenzylidene)indolin-2-one (**Ox31**).* Yellow solid; yield 39%; ratio of diastereoisomers E/Z = 27/73; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 11.1 (br, 1H + 1H, major + minor), 8.64 (s, 1H, major), 8.22 (d, J = 7.3 Hz, 1H, major), 7.95–8.02 (m, 2H, major), 7.77–7.78 (m, 1H, major), 7.24–7.26 (m, 1H, minor), 7.67–7.69 (m, 3H, minor), 7.54–7.61 (m, 3H + 1H, major + minor), 7.04–7.16 (m, 2H, minor), 6.81–6.88 (m, 1H, minor); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 168.2, 167.0, 142.8, 142.2, 139.9, 139.0, 138.1, 136.3, 135.9, 134.8, 134.1, 133.6, 133.4, 131.6, 131.5, 131.2, 131.2, 130.6, 130.4, 129.4, 128.5, 128.2, 127.2, 124.4, 124.2, 122.5, 113.9, 113.4, 113.1, 112.6, 104.1, 103.1; ESI-MS: *m/z* 335.1 ($[M+H]^+$).

*4.2.5.32. (E)-3-(3-chlorobenzylidene)-5-methylindolin-2-one (**Ox32**).* Yellow solid; yield 48%, mp 185–186 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 10.51 (br, 1H), 7.73 (s, 1H), 7.66 (d, J = 6.5 Hz, 1H), 7.52–7.57 (m, 3H), 7.24 (s, 1H), 7.05 (d, J = 7.9 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 168.8, 141.4, 137.2, 134.1, 133.9, 131.4, 131.1, 130.2, 129.7, 129.4, 129.3, 128.1, 123.4, 121.1, 110.5; ESI-MS: *m/z* 270.1 ($[M+H]^+$).

*4.2.5.33. 3-methyleneindolin-2-one (**Ox33**) [53].* To a solution of isatin (1.47 g, 10 mmol, 1.0 eq) in Et_2O (50 mL) was added a solution of $TMSCH_2MgCl$ in Et_2O (1.0 M, 20 mL, 20 mmol, 2.0 eq) at −78°C and the mixture was stirred for 10 min at −78°C then for 12 h at r.t. The reaction was quenched by the addition of MeOH. After removal of the solvent, the residue was purified using column chromatography (petroleum ether/AcOEt = 1:1) to give 3-hydroxy-3-trimethylsilylmethyloxindole. To a solution of 3-hydroxy-3-trimethylsilylmethyloxindole (1.17 g, 5.0 mmol, 1 eq) in DCM (60 mL) was added BF_3OEt_2 (3.2 mL, 25.0 mmol) at −78°C and the mixture was stirred for 2 h at −78°C then for 1 h at 0°C. The reaction was quenched by the addition of saturated $NaHCO_3$ solution and the organic compounds were extracted with DCM and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, **Ox33** was obtained as a yellow solid. Yield 31%, mp 243–245 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (br, 1H), 7.48 (d, J = 7.3 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.01 (d, J = 7.7 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.39 (s, 1H), 6.12 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 178.0, 142.3, 134.9, 127.7, 125.4, 124.6, 122.4, 120.1, 110.3; ESI-MS: *m/z* 146.2 ($[M+H]^+$).

*4.2.6. General procedure for synthesis of N-substituted γ-lactams **Py38-51** [54]*

NaH (40 mg, 1.0 mmol, 60% in paraffin, 1.0 equiv.) was slowly added at 0 °C to a solution of **Py25** (191 mg, 1.0 mmol, 1.0 eq) in 10 mL of dry DMF under N_2. After 15 min stirring at r.t., bromide (1.1 mmol, 1.1 eq) was added dropwise and stirring was continued for 2–3 h at the same temperature until TLC indicated complete consumption of the starting material. The reaction was quenched by the addition of 10 mL water and extracted with AcOEt (3 × 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Pure product was obtained after column chromatography on silica gel (petroleum ether/AcOEt = 8/2).

*4.2.6.1. (E)-1-butyl-3-(2-fluorobenzylidene)pyrrolidin-2-one (**Py38**).* Brown oil, yield 81%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.56 (t, J = 2.7 Hz, 1H), 7.47–7.51 (m, 1H), 7.31–7.35 (m, 1H), 7.11–7.21 (m, 2H), 3.47–3.53 (m, 4H), 3.03 (td, J = 6.5, 2.7 Hz, 2H), 1.59–1.65 (m, 2H), 1.37–1.44 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.5, 160.1, 133.6, 129.8, 129.4, 124.0, 123.9, 121.9, 115.8, 44.4, 43.0, 29.3, 24.4, 20.1, 13.7; ESI-MS: *m/z* 248.3 ($[M+H]^+$).

*4.2.6.2. (E)-3-(2-fluorobenzylidene)-1-pentylpyrrolidin-2-one (**Py39**).* Brown oil, yield 85%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.53 (t, J = 2.6 Hz, 1H), 7.45–7.48 (m, 1H), 7.28–7.33 (m, 1H), 7.09–7.18 (m, 2H), 3.50 (t, J = 6.3 Hz, 2H), 3.45 (t, J = 7.0 Hz, 2H), 3.01 (td, J = 6.5, 2.6 Hz, 2H), 1.58–1.64 (m, 2H), 1.30–1.40 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.5, 160.0, 133.6, 129.8, 129.4, 124.0, 123.9, 121.8, 115.8, 44.4, 43.2, 29.0,

26.9, 24.4, 22.3, 23.9; ESI-MS: *m/z* 262.3 ($[M+H]^+$).

*4.2.6.3. (E)-3-(2-fluorobenzylidene)-1-(4-methylpentyl)pyrrolidin-2-one (**Py40**).* Brown oil, yield 79%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.54 (t, J = 2.7 Hz, 1H), 7.46–7.49 (m, 1H), 7.29–7.33 (m, 1H), 7.09–7.19 (m, 2H), 3.47–3.51 (m, 4H), 3.01 (td, J = 6.5, 2.9 Hz, 2H), 1.59–1.67 (m, 1H), 1.48–1.52 (m, 2H), 0.98 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.4, 160.1, 133.6, 129.9, 129.4, 124.0, 123.9, 121.7, 115.8, 44.3, 41.6, 26.0, 25.9, 24.4, 22.5; ESI-MS: *m/z* 275.3 ($[M+H]^+$).

*4.2.6.4. (E)-1-decyl-3-(2-fluorobenzylidene)pyrrolidin-2-one (**Py41**).* Brown oil, yield 82%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.54 (t, J = 2.7 Hz, 1H), 7.46–7.49 (m, 1H), 7.29–7.34 (m, 1H), 7.10–7.19 (m, 2H), 3.50 (t, J = 6.5 Hz, 2H), 3.45 (t, J = 7.4 Hz, 2H), 3.01 (td, J = 6.5, 2.8 Hz, 2H), 1.56–1.62 (m, 2H), 1.29–1.35 (m, 14H), 0.90 (t, J = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.5, 160.1, 133.6, 129.9, 129.4, 124.0, 123.9, 121.8, 115.8, 44.4, 43.3, 31.9, 29.5, 29.5, 29.3, 29.3, 27.3, 26.9, 24.4, 22.6, 14.1; ESI-MS: *m/z* 331.5 ($[M+H]^+$).

*4.2.6.5. (E)-3-(2-fluorobenzylidene)-1-hexadecylpyrrolidin-2-one (**Py42**).* Brown oil, yield 83%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.54 (t, J = 2.6 Hz, 1H), 7.46–7.49 (m, 1H), 7.29–7.33 (m, 1H), 7.09–7.19 (m, 2H), 3.50 (t, J = 6.2 Hz, 2H), 3.45 (t, J = 7.4 Hz, 2H), 3.01 (td, J = 6.5, 2.8 Hz, 2H), 1.59–1.62 (m, 2H), 1.28–1.34 (m, 26H), 0.90 (t, J = 7.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.5, 160.1, 133.6, 129.8, 129.4, 124.0, 123.9, 121.8, 115.8, 44.4, 43.3, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.3, 27.3, 26.9, 24.4, 22.7, 14.1; ESI-MS: *m/z* 415.3 ($[M+H]^+$).

*4.2.6.6. (E)-1-benzyl-3-(2-fluorobenzylidene)pyrrolidin-2-one (**Py43**).* Brown oil, yield 85%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.64 (t, J = 2.7 Hz, 1H), 7.47–7.50 (m, 1H), 7.30–7.39 (m, 6H), 7.11–7.20 (m, 2H), 4.68 (s, 2H), 3.40 (t, J = 6.6 Hz, 2H), 3.00 (td, J = 6.6, 2.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.5, 160.1, 136.3, 133.2, 130.0, 129.4, 128.7, 128.3, 127.7, 124.0, 123.8, 122.5, 115.9, 47.3, 43.9, 24.2; ESI-MS: *m/z* 271.3 ($[M+H]^+$).

*4.2.6.7. (E)-1-(4-fluorobenzyl)-3-(2-fluorobenzylidene)pyrrolidin-2-one (**Py44**).* Brown oil, yield 86%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.62 (t, J = 2.7 Hz, 1H), 7.46–7.49 (m, 1H), 7.38–7.41 (m, 1H), 7.28–7.35 (m, 2H), 7.08–7.20 (m, 4H), 4.72 (s, 2H), 3.46 (t, J = 8.5 Hz, 2H), 3.01 (td, J = 6.5, 2.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.7, 160.2, 160.1, 132.9, 130.9, 130.0, 129.5, 129.4, 124.5, 123.9, 123.7, 123.3, 122.6, 115.9, 115.5, 44.2, 40.5, 24.3; ESI-MS: *m/z* 299.5 ($[M+H]^+$).

*4.2.6.8. (E)-1-(4-chlorobenzyl)-3-(2-fluorobenzylidene)pyrrolidin-2-one (**Py45**).* Brown oil, yield 85%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.62 (t, J = 2.7 Hz, 1H), 7.46–7.49 (m, 1H), 7.31–7.34 (m, 3H), 7.25–7.27 (m, 2H), 7.11–7.20 (m, 2H), 4.61 (s, 2H), 3.38 (t, J = 6.6 Hz, 2H), 3.00 (td, J = 6.5, 2.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.7, 160.1, 134.9, 133.6, 132.8, 130.1, 129.7, 129.4, 128.9, 124.0, 123.6, 122.8, 115.9, 46.7, 43.9, 24.2; ESI-MS: *m/z* 315.2 ($[M+H]^+$).

*4.2.6.9. (E)-1-(4-bromobenzyl)-3-(2-fluorobenzylidene)pyrrolidin-2-one (**Py46**).* Brown oil, yield 84%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.62 (t, J = 2.7 Hz, 1H), 7.45–7.50 (m, 1H), 7.31–7.36 (m, 1H), 7.24–7.27 (m, 2H), 7.17–7.20 (m, 2H), 4.58 (s, 2H), 3.38 (t, J = 6.6 Hz, 2H), 3.00 (td, J = 6.6, 2.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.7, 160.1, 136.1, 135.3, 132.8, 131.9, 130.1, 130.0, 129.4, 124.0, 123.6, 122.9, 115.9, 46.7, 43.9, 24.2; ESI-MS: *m/z* 360.3 ($[M+H]^+$).

*4.2.6.10. (E)-3-(2-fluorobenzylidene)-1-(4-methylbenzyl)pyrrolidin-2-one (**Py47**).* Brown oil, yield 87%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.62 (t, J = 2.7 Hz, 1H), 7.46–7.49 (m, 1H), 7.29–7.35 (m, 1H), 7.15–7.23 (m, 5H), 7.11–7.15 (m, 1H), 4.61 (s, 2H), 3.38 (t, J = 6.6 Hz, 2H), 3.00 (td, J = 6.5, 2.4 Hz, 2H), 2.37 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.5, 160.1, 137.4, 133.3, 130.0, 129.4, 129.2, 128.3, 127.1, 123.9, 123.8, 122.4, 115.8, 47.1, 43.8, 24.2, 21.1; ESI-MS: *m/z* 295.3 ($[M+H]^+$).

*4.2.6.11. (E)-1-(3-chlorobenzyl)-3-(2-fluorobenzylidene)pyrrolidin-2-one (**Py48**).* Brown oil, yield 81%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.62 (t, J = 2.7 Hz, 1H), 7.46–7.49 (m, 1H), 7.28–7.36 (m, 5H), 7.18–7.22 (m, 2H), 7.12–7.16 (m, 1H), 4.61 (s, 2H), 3.41 (t, J = 6.0 Hz, 2H), 3.02 (td, J = 6.0, 2.4 Hz, 2H), 2.37 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.5, 160.1, 138.4, 134.6, 132.7, 130.1, 130.0, 129.4, 128.3, 127.9, 126.4, 124.0, 122.9, 116.9, 46.8, 44.0, 24.2; ESI-MS: *m/z* 315.2 ($[M+H]^+$).

*4.2.6.12. (E)-1-(3-fluorobenzyl)-3-(2-fluorobenzylidene)pyrrolidin-2-one (**Py49**).* Brown oil, yield 83%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.64 (t, J = 2.7 Hz, 1H), 7.46–7.49 (m, 1H), 7.32–7.36 (m, 2H), 7.10–7.21 (m, 3H), 7.00–7.03 (m, 2H), 4.61 (s, 2H), 3.41 (t, J = 6.7 Hz, 2H), 3.02 (td, J = 6.4, 2.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.7, 162.3, 160.0, 138.9, 132.8, 130.3, 130.2, 129.4, 124.0, 123.8, 123.7, 122.9, 115.9, 115.1, 114.6, 46.9, 44.0, 24.2; ESI-MS: *m/z* 299.5 ($[M+H]^+$).

*4.2.6.13. (E)-1-(2-fluorobenzyl)-3-(2-fluorobenzylidene)pyrrolidin-2-one (**Py50**).* Brown oil, yield 88%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.61 (t, J = 2.7 Hz, 1H), 7.46–7.49 (m, 1H), 7.37–7.40 (m, 1H), 7.28–7.33 (m, 2H), 7.06–7.19 (m, 4H), 4.71 (s, 2H), 3.45 (t, J = 6.5 Hz, 2H), 2.99 (td, J = 6.6, 2.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.7, 162.0, 160.0, 138.9, 132.9, 130.8, 130.1, 129.5, 129.4, 124.5, 124.0, 123.8, 123.3, 122.5, 115.8, 115.4, 44.1, 40.5, 24.3; ESI-MS: *m/z* 299.5 ($[M+H]^+$).

*4.2.6.14. (E)-1-(2,6-dichlorobenzyl)-3-(2-fluorobenzylidene)pyrrolidin-2-one (**Py51**).* Brown oil, yield 83%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.63 (t, J = 2.7 Hz, 1H), 7.45–7.48 (m, 1H), 7.38–7.40 (m, 2H), 7.31–7.35 (m, 1H), 7.24–7.27 (m, 1H), 7.11–7.19 (m, 2H), 5.02 (s, 2H), 3.31 (t, J = 6.6 Hz, 2H), 2.96 (td, J = 6.5, 2.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 168.7, 162.0, 136.8, 132.8, 131.2, 130.0, 129.9, 129.9, 129.8, 129.4, 128.5, 123.9, 123.8, 122.5, 115.8, 43.2, 42.4, 24.2; ESI-MS: *m/z* 350.3 ($[M+H]^+$).

*4.2.7. General procedure for synthesis of **La1-3***

*4.2.7.1. N-substituted γ-lactam (**11a-c**) [74].* To a suspension of NaH (0.80 g, 20.0 mmol, 1.0 eq) in THF (40 mL) at 0 °C was added pyrrolidone (1.70 g, 20 mmol, 1.0 eq) and the reaction mixture stirred therein for 30 min. The reaction was then warmed to r.t. and left to stir for a further 30 min until H_2 ceased to evolve. Benzyl bromide (20 mmol, 1.0 eq) was added dropwise and the reaction stirred for 12 h. The reaction was quenched by the addition of H_2O (500 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried and concentrated in vacuo to give desired product.

*4.2.7.2. 1-Benzylpyrrolidin-2-one (**11a**) [75].* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.23–7.36 (m, 5H), 4.45 (s, 2H), 3.25–3.29 (m, 2H), 2.42–2.48 (m, 2H), 1.95–2.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 175.0, 136.5, 128.6, 128.1, 127.5, 46.3, 45.9, 30.9, 17.7; ESI-MS: *m/z* 176.1 ($[M+H]^+$).

*4.2.7.3. 1-(4-Chlorobenzyl)pyrrolidin-2-one (**11b**) [75].* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.15–7.16 (m, 4H), 4.44 (s, 2H),

3.25–3.29 (m, 2H), 2.43–2.48 (m, 2H), 2.36 (s, 3H), 1.97–2.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 174.9, 137.2, 133.5, 129.3, 128.1, 46.5, 46.3, 31.0, 21.1, 17.7; ESI-MS: *m/z* 210.7 ($[M+H]^+$).

*4.2.7.4. 1-(4-Methylbenzyl)pyrrolidin-2-one (**11c**) [75].* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.18–7.31 (m, 4H), 4.42 (s, 2H), 3.25–3.29 (m, 2H), 2.42–2.46 (m, 2H), 1.97–2.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 175.0, 135.1, 133.3, 129.4, 128.8, 46.6, 45.9, 30.8, 17.7; ESI-MS: *m/z* 190.2 ($[M+H]^+$).

*4.2.7.5. N-substituted α-methylene-γ-lactam (**La1-3**) [51,52].* A solution of LDA was prepared by the addition of diisopropylamine (1.4 mL, 10 mmol, 2.0 eq) to a stirred solution of *n*-BuLi (1.6 M in Hexanes, 6.3 mL, 10 mmol, 2.0 eq) in THF (2.5 mL) at -5 °C, and the resultant solution was stirred for 30 min. A solution of 1-benzylpyrrolidin-2-one (875.5 mg, 5 mmol, 1.0 eq) in THF (5 ml) was then added via cannula, and the temperature rose to 15 °C and the solution stirred for 10 min. A solution of diethylchlorophosphate (0.75 mL, 5 mmol, 1.0 eq) in THF (4 mL) was then added via cannula. The resulting solution was stirred at room temperature for 3 h. The solution was then acidified to pH 1 (1 M aqueous HCl), and the aqueous layer was separated and extracted with DCM (3 × 10 mL). The combined organic extracts were dried and concentrated in vacuo to give the crude product. Purification by column chromatography (petroleum ether/AcOEt = 1/1) gave 1-benzyl-3-(diethoxyphosphinyl)-pyrrolidin-2-one as a brown oil. To a solution of 1-benzyl-3-(diethoxyphosphinyl)-pyrrolidin-2-one (311 mg, 1.0 mmol, 1.0 eq) in THF (5 mL) was added NaH (33 mg, 1.1 mmol, 1.1 eq) at 0°C, and the reaction mixture was stirred for 0.5 h. Then, paraformaldehyde (0.330 g, 1.1 mmol) was added at 0°C and the mixture was stirred for 1.5 h at room temperature. After that, brine (5 mL) was added, and the mixture was extracted with DCM (3 × 10 mL). Combined organic extracts were dried and evaporated to give crude product which was purified by column chromatography (petroleum ether/AcOEt = 5/1).

*4.2.7.6. 1-Benzyl-3-methylenepyrrolidin-2-one (**La1**).* Light yellow oil, yield 31%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.25–7.34 (m, 5H), 6.03 (t, *J* = 2.4 Hz, 1H), 5.35 (t, *J* = 2.4 Hz, 1H), 4.55 (s, 2H), 3.27 (t, *J* = 7.0 Hz, 2H), 2.71–2.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 167.9, 139.6, 136.3, 128.7, 128.3, 127.6, 115.7, 47.3, 43.5, 23.9; ESI-MS: *m/z* 187.3 ($[M+H]^+$).

*4.2.7.7. 1-(4-Methylbenzyl)-3-methylenepyrrolidin-2-one (**La2**).* Brown oil, yield 29%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.14–7.18 (m, 4H), 6.04 (t, *J* = 2.6 Hz, 1H), 5.36 (t, *J* = 2.6 Hz, 1H), 4.52 (s, 2H), 3.27 (t, *J* = 7.0 Hz, 2H), 2.71–2.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 167.8, 139.7, 137.3, 133.2, 129.3, 128.3, 115.2, 46.9, 43.4, 23.9, 21.1; ESI-MS: *m/z* 210.3 ($[M+H]^+$).

*4.2.7.8. 1-(4-Chlorobenzyl)-3-methylenepyrrolidin-2-one (**La3**).* Brown oil, yield 33%; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.23–7.34 (m, 5H), 6.08 (t, *J* = 2.5 Hz, 1H), 5.41 (t, *J* = 2.4 Hz, 1H), 4.55 (s, 2H), 3.30 (t, *J* = 7.0 Hz, 2H), 2.76–2.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 167.9, 139.3, 134.8, 133.5, 129.6, 128.9, 116.0, 46.6, 43.4, 23.9; ESI-MS: *m/z* 221.2 ($[M+H]^+$).

4.3. Antifungal activity in vitro tested on spore germination [21,76,77]

The fungal pathogen *F. graminearum* Schw., *C. orbiculare*, *B. cinerea*, *F. oxysporum*, and *C. gloeosporioides* Penz. were provided by Research & Development Center of Biorational Pesticide, Northwest A&F University. Those isolates were cultured for 2 weeks at 25 ± 1 °C on potato dextrose agar (PDA) after being retrieved from the storage tube. Plates were then flooded with sterile distilled water, and then conidia were scraped with a glass rod. Mycelial debris was removed by filtration through double-layer cheesecloth. The spores were harvested and suspended in sterile distilled water containing 0.1% (v/v) Tween 20. Concentration of the spore suspension was adjusted to 1.0×10^6 spore/mL by diluting with sterilized distilled water using a SUPERIOR hemocytometer.

The tested samples (10 mg) dissolved in dimethyl sulfoxide or acetone (0.1 mL) were diluted with sterile distilled water to prepare 10 mL stock solution, which was further diluted to prepare test solutions in which the final concentration of acetone was <0.5% (v/v). A series of concentrations of tested samples and one control (0.5% dimethyl sulfoxide or acetone with sterile distilled water) were separately tested for spore germination. The samples were inoculated with spore suspension containing 1.0×10^6 spores/mL. Aliquots of 50 μL of prepared spore suspension were placed on separate glass slides in triplicate. Slides containing the spores were incubated in a moisture chamber at 25 °C for 6–8 h. Each slide was then observed under the microscope for spore germination. Spores were considered to have germinated if the length of the germ tube was at least half the length of the spore. Afterward, spore germination was stopped by applying a drop of lactophenol-cotton blue to the inoculation sites on plates. The numbers of generated spores were counted (three replicates were conducted for each treatment, and a minimum of 200 spores were counted in each replicate) under a microscope (Olympus BX61, Tokyo, Japan), and the percentage of germinated spores was calculated. The inhibition ratio (%) was determined according to the Abbott's formula: 100 × [(the average percentage of spore germinated of the control − the average percentage of spore germinated of treatment)/the average percentage of spore germinated of the control]. This experiment was repeated three times under the same conditions. Carbendazim (Fig. 5) was used as the positive control.

4.4. Cytotoxicity assay [78]

Cytotoxicity of all the tested compounds against HepG2 cell and human hepatic L02 cells were determined by means of the colorimetric assay CCK-8 (Beyotime, Beijing, China). The assay was carried out according to the Technical Manual of the Kit (http://www.dojindo.com/TechnicalManual/Manual_CK04.pdf). In general, the cells were plated in 96-well culture plates at density of 1×10^4 cells per well and incubated for 24 h at 37 °C in the atmosphere (5% CO_2). The compounds with six desired concentrations were obtained by dissolving in DMSO and diluting with culture medium (DMSO final concentration < 0.4%). The background control and blank control was prepared with the culture medium. Then the diluted solution of tested compounds or the blank control was treated with the cells for 24 h at 37 °C in a 5% CO_2 incubator, and the background control was treated without the cells. After that, 10 μL of a freshly CCK-8 solution were added to each well and the plates were incubated for 2 h. The cell survival was evaluated by measuring the absorbance at 450 nm and calculated by the formula (cell viability =

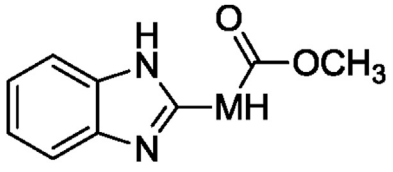


Fig. 5. The chemical structure of reference compound carbendazim in the antifungal tests.

(ODtested - ODbackground control)/OD blank control). IC_{50} values were determined from the chart of cell viability (%) against compound concentration (μM). All experiments were carried out in triplicate.

4.5. Statistical analysis

The experimental data were all analyzed using SPSS 16.0 for Windows.

4.6. Ultrastructural changes study by transmission electron microscopy (TEM)

Spores were cultured in PDB medium. After germination, compound **Py51** was incubated to get a final concentration of 55 μM (IC_{90}) (or 0.5% DMSO). After 12, 24, 48 and 72 h incubations, the medium were centrifugated to obtain the specimens. TEM was performed according to the reported standard procedure with some modification [79]. Briefly, specimens were harvested and fixed with 3% glutaraldehyde 24 h in the dark. After being washed with 1 M PBS (phosphate buffered saline, pH 7.2) three times (15 min each), specimens were postfixed in reduced osmium tetroxide (1% OsO_4) for 2 h. After three washing steps (15 min each), cells were dehydrated in a standard acetone series (30 min each) and embedded in Spurr's low-viscosity resin 12 h at 45°C. Ultrathin sections (40–60 nm) were cut with a Leica Ultracut RM2265 (Leica, Vienna, Austria), mounted on regular hexagonal copper grids, stained with lead citrate (10 min), washed three times with decarbon dioxide deuterium depleted water (ddw) and stained with uranyl acetate 30 min, washed with ddw three times and examined with a JEOL JEM-1230 transmission electron microscope.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2017.02.050.

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