Tetrahedron 71 (2015) 6961–6978

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of α-ketols by functionalization of captodative alkenes and divergent preparation of heterocycles and natural products

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ARTICLE INFO

Article history:
Received 24 March 2015
Received in revised form 2 July 2015
Accepted 3 July 2015
Available online 9 July 2015

Keywords:
Captodative alkenes
1-Acetylvinyl *p*-nitrobenzoyloxy
α-Ketols
Actinopolymorphol B
Tanakine
4-Oxazolin-2-ones

ABSTRACT

Captodative alkene 1-acetylvinyl *p*-nitrobenzenecarboxylate **1a** was evaluated for its reactivity in Lewis acid-catalyzed Michael additions with functionalized benzene rings and heterocycles, leading to diverse conjugated addition adducts. The hydrolysis of the latter resulted in the desired functionalized α-ketols, including natural alkaloid actinopolymorphol B (**24a**). The α-ketol core structure of these compounds was used as the building block for the synthesis of the natural alkaloid tanakine (**25**) and for the divergent construction of highly substituted heterocycles, such as 4-oxazolin-2-ones and butenolides, and their respective fused polycyclic derivatives.

1. Introduction

Heterocyclic structural units occur in many bioactive natural products and synthetic drugs, and they are useful key intermediates for developing novel methodologies to synthesize natural products. One class of heterocycles formed by butenolides[1] and oxazolin-2-ones[2] has received extensive attention owing to their potential as versatile synthons and their presence in a large number of natural products and pharmacologically active agents. Although numerous methods have been designed to construct these heterocycles,[3,4] one of the most straightforward approaches starts from α-ketols (acyloins).[5]

The study of the behavior of α-ketols is of considerable interest due to their diverse and often stereospecific rearrangements leading to isomeric products.[6] From a synthetic point of view, the 1,2-migrations of the substituents in a cyclic α-ketol can be a useful strategy to yield newly formed cyclic α-ketols that have been expanded or contracted, and these in turn can be employed as multifaceted synthons.[7] Due to this advantageous behavior of α-ketols, together with their presence in natural products,[8] and their applications in the synthesis of heterocycles[9] many synthetic protocols have been developed for their preparation,[10] including biocatalytic asymmetric approaches.[11]

We previously reported a direct method for generating α-ketols **4**[12] via regio- and stereoselective Diels–Alder cycloadditions of the captodative alkenes 1-acetylvinyl carboxylates **1** with dienes **2** (Scheme 1). Moreover, the α-ketols **4** obtained were used in the preparation of the corresponding γ-hydroxycyclohexenones **8** through an epoxidation/Baeyer–Villiger/hydrolysis cascade reaction with *m*-chloroperbenzoic acid (MCPBA),[13] as well as in approaches for synthetizing natural products.[5d,14] We also reported the preliminary results of an alternative method for obtaining α-ketols **7** by taking advantage of the suitable reactivity of alkenes **1** under Friedel–Crafts conditions.[15]

Captodative alkenes **1** have attracted particular theoretical interest[16] due to the opposite electron-demand displayed by their geminally substituted functional groups in the double bond.[17] This interest has been principally focused on their reactivity and stereo- and regioselectivity in [4+2] cycloaddition reactions.[12,14b,18]

As an extension of our previous report, a broad study of the application of alkenes **1** in the synthesis of substituted α-ketols is herein described. Additionally, the present work discloses the use of α-ketols as precursors in a divergent approach for constructing novel butenolides and 4-oxazolin-2-ones, as well as in a very short and efficient total synthesis of the α-hydroxy ketone natural

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http://dx.doi.org/10.1016/j.tet.2015.07.010
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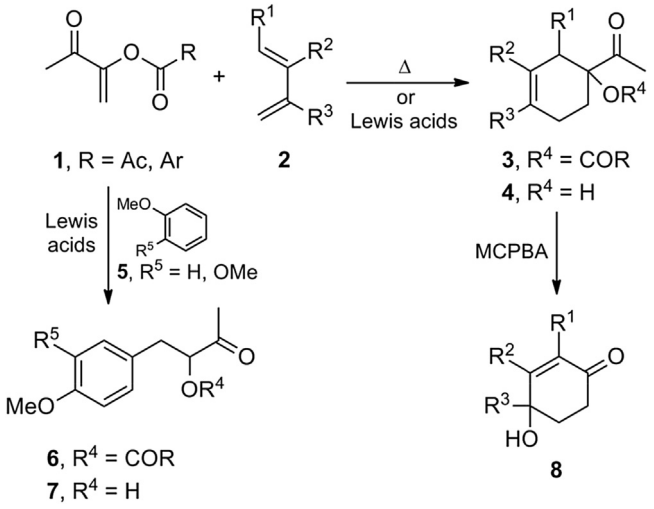


Scheme 1. Reactivity and synthetic applications of captodative alkenes **1**.

product actinopolymorphol B (**24a**)[19] and the related 3-indolyl diol tanakine (**25**).[20]

2. Results and discussion

2.1. Synthesis of α-ketols and their conversion into 4-oxazolin-2-ones

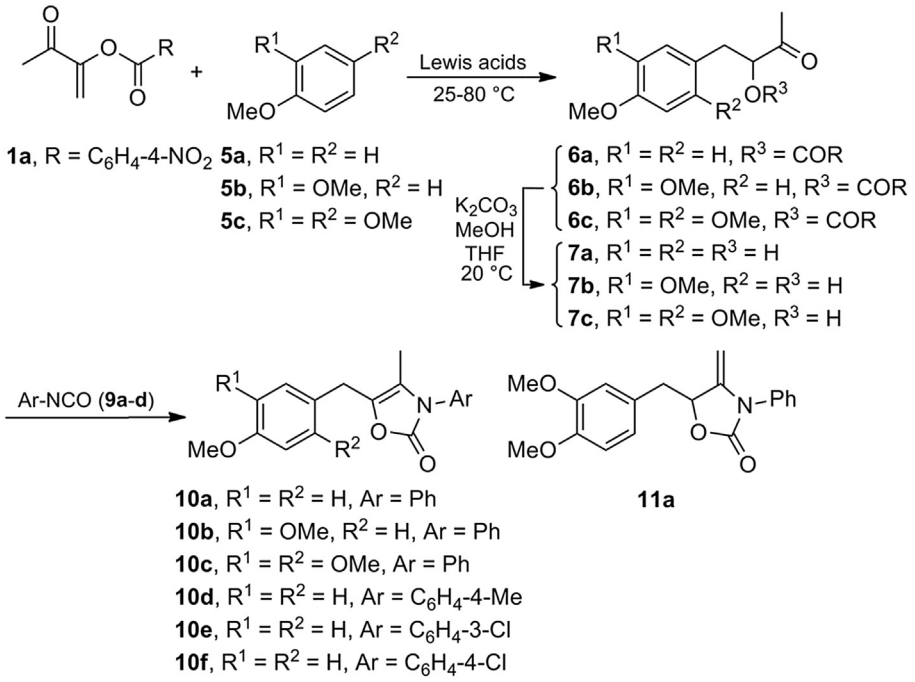
We previously reported a preliminary study of the Lewis acid-catalyzed Friedel–Crafts reactions of olefin **1a** with an excess of the activated benzenes **5a**–**c** to give the corresponding adducts **6a**–**c** (Scheme 2) in high yields (Table 1, entries 1–3).[15] A lower amount of **5a**–**c** adversely affected the yields. In spite of this disadvantage, the excess of the starting material could be easily recovered during the purification of the reaction mixtures by column chromatography. With a base-promoted hydrolysis of the latter, α-ketols **7a**–**c** were obtained in good yields (68–92%) (Table 2, entries 1–3).

Table 1
Preparation of adducts **6a**–**c**, **13a**–**d**, **14a**,**b**, and **20a**–**e** by Lewis acid- or DMAP-catalyzed conjugated additions of nucleophiles (Nu) **5a**–**c**, **12a**–**d** or **19a**–**e** to **1a**[a]

Entry	Nu (mol equiv)	Catalyst (mol equiv)	*T* (°C)	*t* (h)	Product	Yield[b] (%)
1	**5a** (10)	$BF_3{\cdot}Et_2O$ (2.0)	25	48	**6a**	75[c]
2	**5b** (5)	$BF_3{\cdot}Et_2O$ (10.0)	10	48	**6b**	85[c]
3	**5c** (10)	$AlCl_3$ (1.0)	25	0.5	**6c**	81[c]
4	**12a** (10)	$BF_3{\cdot}Et_2O$ (4.1)	25	1	**13a**	60
5	**12a** (10)	$TiCl_4$ (1.8)	25	1	**13a**	63
6	**12a** (10)	$AlCl_3$ (0.5)	25	8	**13a**	74
7	**12a** (10)	$ZnCl_2$ (5.0)	25	72	**13a**	55
8	**12a** (10)	ZnI_2 (5.0)	40	54	**13a**	62
9	**12b** (10)	$BF_3{\cdot}Et_2O$ (4.8)	25	5	**13b**	85
10	**12c** (10)	$BF_3{\cdot}Et_2O$ (5.0)	25	6	**13c**	68
11	**12d** (1.0)	$AlCl_3$ (1.2)	25	1	**13d**	28
12	**12d** (4.0)	I_2 (0.05)	25	5	**13d**	48
13[d]	**12a** (1.0)	$BF_3{\cdot}Et_2O$ (4.4)	25	2	**14a**	80
14[d]	**12b** (1.0)	$BF_3{\cdot}Et_2O$ (8.2)	25	120	**14b**	75
15	**19a** (1.1)	DMAP (0.4)	25	2	**20a**	92
16	**19b** (1.1)	DMAP (0.4)	25	3	**20b**	95
17	**19c** (1.1)	DMAP (0.4)	25	3	**20c**	92
18	**19d** (1.1)	DMAP (0.4)	25	3	**20d**	90
19	**19e** (1.1)	DMAP (0.4)	25	3	**20e**	80

[a] All under N_2 atmosphere, with 1.0 mol equiv of **1a**, in CH_2Cl_2 as the solvent.
[b] After column chromatography.
[c] See Ref. 15.
[d] With 2.0 mol equiv of **1a**.

Following the method of the microwave (MW)-irradiation-mediated preparation of 4-oxazolin-2-ones starting from α-ketols,[5b] the series of α-ketols **7a**–**c** was converted into 4-oxazolin-2-ones **10a**–**c** in good yields, using a solvent-free treatment with isocyanate **9a** (Table 3, entries 1–3). This conversion could be carried out at high MW potency (using an SEV reactor), and also at low MW potency (using a CEM reactor), the latter being the case for heterocycle **10f** (entry 6). Apart from evaluating this MW potency range in order to optimize yields, conventional heating was used with the reaction between **7a** and isocyanates **9b**,**c**, affording the expected products **10d**,**e**, although this implies longer reaction times and lower yields (Table 3, entries 4 and 5). In some assays the amount of isocyanates was increased to restore that consumed during the conversion into the respective products as well as urea



Scheme 2. Lewis acid-catalyzed Friedel–Crafts reactions of olefin **1a** with activated benzenes **5a**–**c**.

Table 2
Preparation of α-ketols **7a**–**c**, **15a**–**d**, **16a**,**b**, and **21a**–**e** via a base-catalyzed hydrolysis of esters **6a**–**c**, **13a**–**d**, **14a**,**b**, and **20a**–**e**, respectively[a]

Entry	Ester	Catalyst (mol equiv)	Solvent	*t* (min)	Product	Yield[b] (%)
1	**6a**	K_2CO_3 (4.0)	MeOH/THF	10	**7a**	90[c]
2	**6b**	K_2CO_3 (4.0)	MeOH/THF	60	**7b**	68[c]
3	**6c**	K_2CO_3 (4.0)	MeOH/THF	20	**7c**	92
4	**13a**	K_2CO_3 (3.0)	MeOH/THF	30	**15a**	86
5	**13b**	K_2CO_3 (3.0)	MeOH/THF	90	**15b**	94
6	**13c**	K_2CO_3 (3.0)	MeOH/THF	15	**15c**	90
7	**13d**	K_2CO_3 (3.0)	MeOH/THF	20	**15d**	84
8	**14a**	K_2CO_3 (4.0)	MeOH/THF	20	**16a**	85
9	**14b**	K_2CO_3 (4.0)	MeOH/THF	20	**16b**	82
10	**20a**	Li_2CO_3 (2.0)	DMF/THF	24[d]	**21a**	85
11	**20b**	Li $_2CO_3$ (2.0)	DMF/THF	24[d]	**21b**	86
12	**20c**	Li $_2CO_3$ (2.0)	DMF/THF	24[d]	**21c**	83
13	**20d**	Li $_2CO_3$ (2.0)	DMF/THF	24[d]	**21d**	85
14	**20e**	Li $_2CO_3$ (2.0)	DMF/THF	24[d]	**21e**	88

[a] All under N_2 atmosphere, with dry K_2CO_3 in a mixture of MeOH/THF (ca.1:3) or dry Li_2CO_3 in a mixture of MeOH/DMF (1:1), at room temperature.
[b] After column chromatography.
[c] See Ref. 15.
[d] Reaction time in hours.

were also efficient aromatic nucleophiles with alkene **1a**, leading to the corresponding adducts **13b**,**c** (Table 1, entries 9 and 10). In some cases a large amount of the catalyst was used in order to improve the yields, considering the several potential binding sites on both alkene **1a** and the heterocycle as well as the diverse factors that may inhibit its catalytic action, as previously observed.[12b] However, pyrrole (**12d**) was not reactive with these catalysts, except that with $AlCl_3$ it furnished the expected adduct **13d** in low yield (Table 1, entry 11). Iodine was a more efficient catalyst, affording **13d** in a better yield (Table 1, entry 12). It is noteworthy that the $BF_3{\cdot}OEt_2$-catalyzed reactions of **12a**,**b** with 2 mol equiv of **1a** provided the corresponding bis-adducts **14a**,**b** in high yields (Table 1, entries 13 and 14). In contrast, pyrrole (**12d**) did not react twice to give bis-adduct **14c**, even in the presence of iodine. The lower reactivity of **12d** compared to heterocycles **12a**,**b** may be associated with the aromaticity of the ring[21] or the basicity of the nitrogen atom of **12d**. The latter may promote the formation of a complex with the Lewis acid, thus inhibiting the activation of the aromatic ring.

The base-promoted hydrolysis of the series **13a**–**d** and **14a**,**b** afforded α-ketols **15a**–**d** and **16a**,**b**, respectively (Scheme 3), in high

Table 3
Preparation of 4-oxazolin-2-ones **10a**–**f**, **11a**, **17a**–**d**, **18a**,**b**, and **22a**–**g** from α-ketols **7a**–**c**, **15a**,**b**, **15d**, **16a**,**b**, **21a**,**b**, and **21d**,**e**, respectively, and isocyanates **9a**–**e**[a]

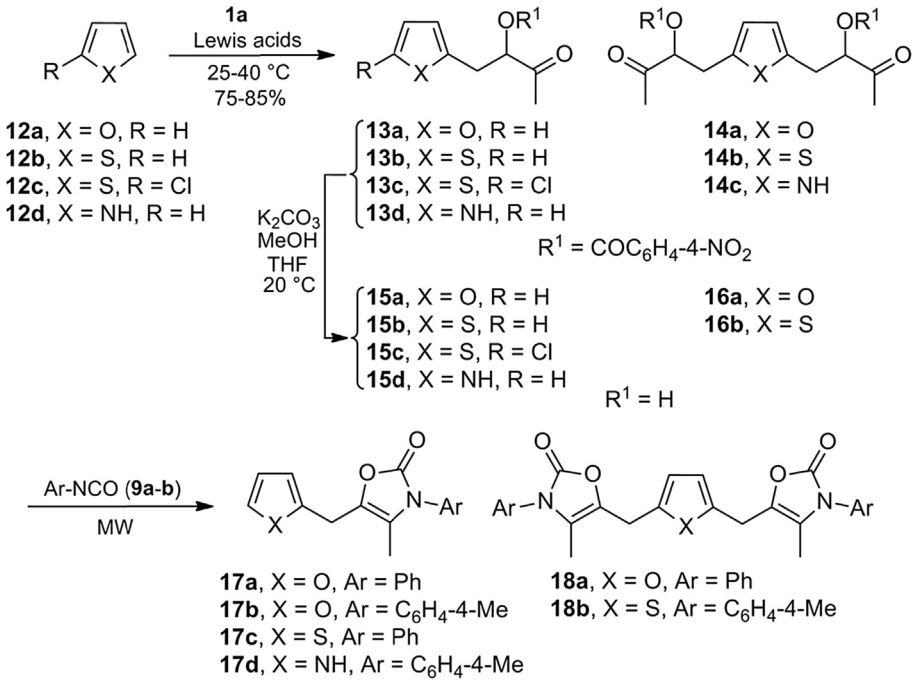
Entry	α-Ketol	**9** (R) (mol equiv)	MW[b] (W)	*T* (°C)	*t* (min)	Product	Yield[c] (%)
1	**7a**	**9a** (Ph) (1.3)	900	80	20	**10a**	70
2	**7b**	**9a** (Ph) (1.3)	900	80	20	**10b**	68
3	**7c**	**9a** (Ph) (1.4)	900	80	20	**10c**	78
4	**7a**	**9b** (C_6H_4-4-Me) (2.4)	—	120	24[d]	**10d**	64
5	**7a**	**9c** (C_6H_4-3-Cl) (1.5)	—	120	24[d]	**10e**	52
6	**7a**	**9d** (C_6H_4-4-Cl) (2.0)	30	120	60	**10f**	63
7	**7b**	**9a** (Ph) (1.3)	200[e]	80	20	**11a**	75
8	**15a**	**9a** (Ph) (1.5)	900	80	20	**17a**	74
9	**15a**	**9b** (C_6H_4-4-Me) (2.4)	—	120	24[d]	**17b**	70
10	**15b**	**9a** (Ph) (1.2)	900	80	20	**17c**	80
11	**15d**	**9b** (C_6H_4-4-Me) (2.4)	30	120	60	**17d**	65
12	**16a**	**9a** (Ph) (2.2)	900	80	20	**18a**	54
13	**16b**	**9b** (C_6H_4-4-Me) (3.0)	30	120	30	**18b**	51
14	**21a**	**9c** (C_6H_4-3-Cl) (1.3)	100	100	40	**22a**	63
15	**21b**	**9a** (Ph) (2.4)	300	120	40	**22b**	57
16	**21b**	**9b** (C_6H_4-4-Me) (2.4)	300	120	40	**22c**	74
17	**21b**	**9e** (C_6H_4-4-OMe) (2.4)	300	120	40	**22d**	74
18	**21d**	**9b** (C_6H_4-4-Me) (2.4)	300	120	40	**22e**	69
19	**21d**	**9e** (C_6H_4-4-OMe) (2.4)	300	120	40	**22f**	61
20	**21e**	**9b** (C_6H_4-4-Me) (2.4)	300	120	40	**22g**	63

[a] All under N_2 atmosphere and with 0.01 mol equiv of hydroquinone for the thermal trial.
[b] The MW (900) irradiation was carried out with the SEV reactor and lower potency irradiations with the CEM reactor.
[c] After column chromatography.
[d] Reaction time in hours.
[e] MW irradiation was carried out with the SEV reactor.

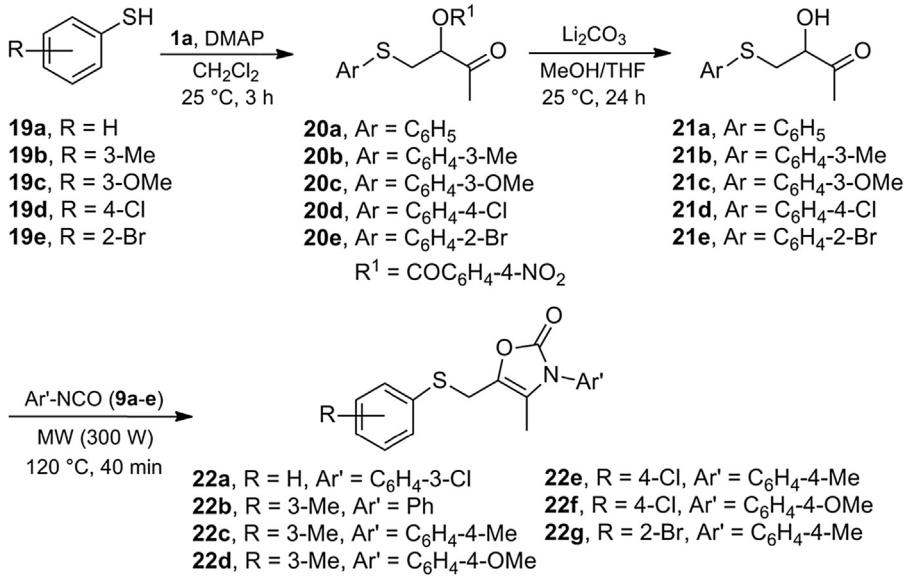
as the main by-product. When **7b** was irradiated under milder conditions (200 W) in the presence of **9a** (Table 3, entry 7), 4-methyleneoxazolidin-2-one **11a** was obtained as the major product in good yield (75%). This is noteworthy since with a thermal or acid-promotion the latter exocyclic isomer could be converted into the endocyclic isomer in an easy and almost quantitative process.[5] Hence, the exocyclic isomer **11a** corresponds to the kinetic product of the reaction, whilst 4-oxazolin-2-one **10b** is the thermodynamic one.

With the aim of evaluating the scope of this methodology, five-membered mono-heteroatom heterocycles **12a**–**d** were also reacted with alkene **1a** (Scheme 3). An excess of the former starting materials was also used and a series of Lewis acid catalysts were evaluated in order to improve the efficiency of the conjugated addition. In the case of furan (**12a**), the Lewis acid-promoted addition to **1a** afforded the monoadduct **13a** in moderate to good yields (Table 1, entries 4–8). $AlCl_3$ was the most efficient catalyst, although the shortest reaction times were obtained by using catalysts $BF_3{\cdot}OEt_2$ and $TiCl_4$. Thiophene (**12b**) and 2-chlorothiophene (**12c**) yields (Table 2, entries 4–9). Some of the members of these series were treated with isocyanates **9a**,**b** for the preparation of the respective 4-oxazolin-2-ones by employing the solvent-free MW-assisted method. As a result, the series of derivatives **17a**–**d** and bis-oxazolinones **18a**,**b** were obtained in moderate to good yields (Table 3, entries 8–13). When the reaction between **15a** and **9b** was thermally heated, a comparable yield of **17b** was observed (Table 3, entry 9).

Since the previously prepared α-ketols were derived from the carbon–carbon bond formation of the corresponding adducts between alkene **1a**, aromatic substituted benzene rings, and five-membered heterocycles, we also investigated the preparation of α-ketols **21a**–**e** from adducts **20a**–**e**, the latter originating from a heteroatom–carbon bond formation (Scheme 4). In spite of the possible addition of thiols to the ester group of alkene **1a**, the series of benzenethiols **19a**–**e** reacted satisfactorily in the presence of catalytic amounts of DMAP and under mild reaction conditions, to give the series of conjugated addition products **20a**–**e** in high yields (Table 1, entries 15–19). Consecutive hydrolysis of



Scheme 3. Lewis acid-catalyzed Friedel–Crafts reactions of olefin **1a** with heterocycles **12a**–**d**.



Scheme 4. Michael addition of benzenethiols **19a**–**e** to alkene **1a**.

the latter series of esters using lithium carbonate as the base under gentle reaction conditions afforded the series of α-ketols **21a**–**e** in high yields (Table 2, entries 10–14). Finally, the treatment of this series with diverse isocyanates, **9a**–**c** and **9e**, resulted in the series of 4-oxazolin-2-ones **22a**–**g** in moderate to good yields (Table 3, entries 14–20). Unfortunately, the isomeric product with the exocyclic double bond, such as the kinetic compound **11a**, could not be obtained as the main product. When using a lower temperature (80–100 °C) for the MW irradiation, the presence of the exocyclic isomer was detected by NMR as small signals in the crude reaction mixture, but it could not be isolated by chromatographic methods due to the presence of additional by-products.

2.2. Expeditious total synthesis of the α-ketol natural product actinopolymorphol B (24a) and the related 3-indolyl diol tanakine (25)

Actinopolymorphol B (**24a**) is an indole alkaloid substituted at the C-3 position by an α-ketol side-chain (Fig. 1) isolated from *Actinopolymorpha rutilus* (YIM45725).[19] Some of the related naturally occurring substituted benzene compounds, such as sattabacin, 4-hydroxysattabacin and kurasoin A, or the C-3 substituted α-ketol side-chain indoles, such as **24b**,**c** (Fig. 1),[22] exhibit significant antioxidant, cytotoxic, and antiviral activities, as well as the inhibition of farnesyltransferase.[22,23] Their structural resemblance to **24a** may anticipate an analogous activity for this as yet untested compound.

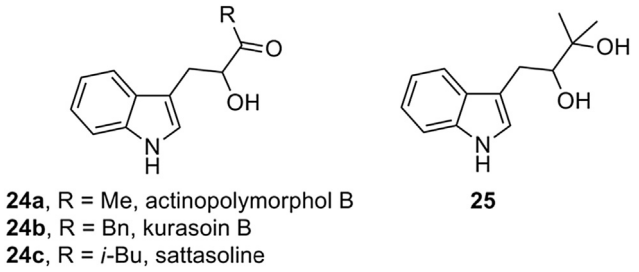


Fig. 1. Indole natural products containing an α-ketol or a diol side-chain.

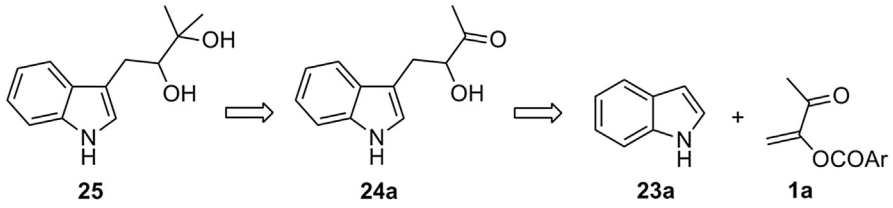
The first total synthesis of **24a** was recently described in a seven-step approach with a 15% overall yield.[23a] Tanakine (**25**), structurally related to **24a**, is an indole substituted at the C-3 position by a diol side-chain.[20] To the best of our knowledge, the synthesis of **25** has not yet been reported. Its preparation may be conceived as a simple addition of a Grignard or lithium methylide reagent to **24a** (Scheme 5).

and in only two steps. The addition of an excess (5.0 mol equiv) of methyl magnesium bromide to **24a** led to natural product **25** in 60% yield (Scheme 6). Spectroscopic data of the latter compounds are in agreement with those reported for the structures of the corresponding natural and synthetic products.[19,20,23a]

In order to evaluate the scope of this methodology and the variety of substrates, and by applying the same reaction conditions as those used for **24a**, the series of *N*-substituted indoles **23b**–**d** was transformed into α-ketols **24b**–**d** via the corresponding esters **26b**–**d**, obtained in moderate to good overall yields (Scheme 6). The shortness and efficiency of this synthetic strategy to afford the series of α-ketols **24a**–**d** may stimulate interest in testing the biological activity of these potential pharmacological agents.

2.3. Preparation of heterocyclic derivatives of α-ketol 24a

α-Ketol alkaloid **24a** was evaluated as the key substrate for the construction of polyheterocyclic compounds. Thus, the MW-assisted reaction of **24a** with isocyanates **9b**,**c** at 120 °C for 1 h

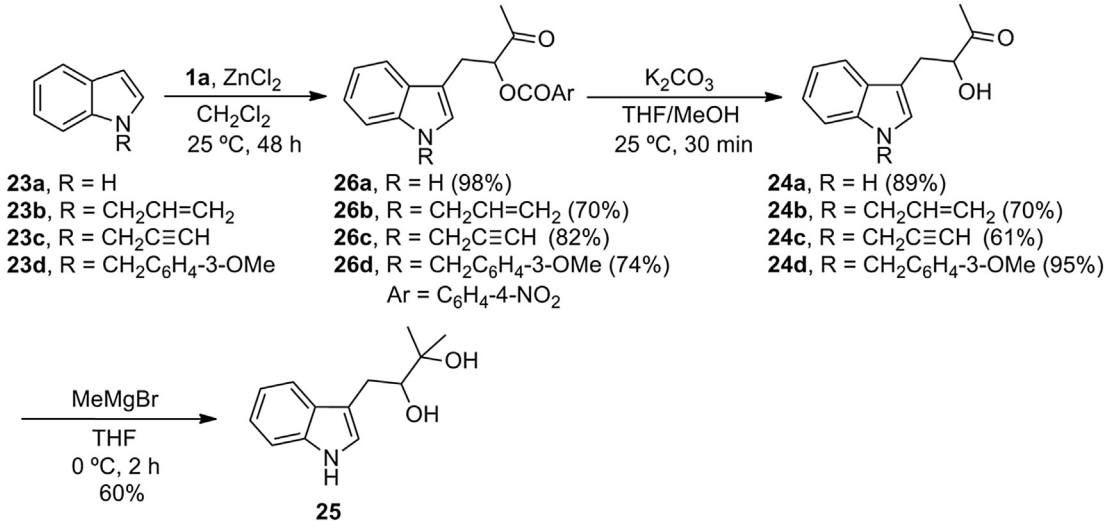


Scheme 5. Retrosynthesis of natural products **24a** and **25**.

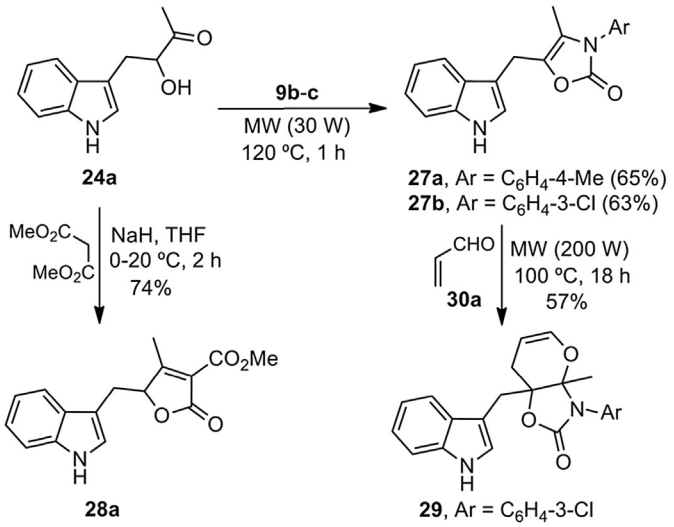
Considering the reactivity of captodative alkene **1a** with nucleophiles (e.g., activated benzene derivatives **5a**–**c**) to yield the corresponding conjugated adducts (Scheme 2), the synthesis of **24a** was designed on the basis of a two-step approach starting from a Lewis acid-catalyzed addition of indole (**23a**) to alkene **1a** (Scheme 5).[24]

For the first step, consisting of the conjugated addition of **23a** to olefin **1a**, many of the Lewis acids shown in Table 1 were evaluated as catalysts, including iodine since it was the most efficient catalyst for the reaction with pyrrole (Scheme 6). However, all of these catalysts were inefficient, although $BF_3{\cdot}Et_2O$ provided the desired adduct **26a** in 60% yield. Overall, the most efficient catalyst was $ZnCl_2$, affording **26a** in 98% yield. The base-assisted hydrolysis of the latter resulted in the natural product **24a** in 87% overall yield, led to the bis-heterocycles **27a**,**b** in moderate yields (Scheme 7). The structure of **27a** was unambiguously established by X-ray diffraction crystallography (Fig. 2), which shows the folding of the heterocycles with each other to adopt a closely orthogonal conformation, as well as a similar conformation for the *N*-aryl ring and the plane formed by the 4-oxazolin-2-one ring. This structure not only corroborates the fact that the 4-oxazoline-2-one scaffold was obtained, but also confirms the substitution of the captodative alkene **1a** at the C-3 of the indole.

We previously used an α-ketol for the formation of the natural occurring butenolide andirolactone,[5d] through condensation with dimethyl malonate under basic conditions. This methodology was useful for the same conversion when starting from **24a**, and has been recently applied to the synthesis of a variety of products.[25]



Scheme 6. Synthesis of natural alkaloids **24a** and **25**, and the series of the indolyl α-ketols **24b**–**d**.



Scheme 7. Transformation of alkaloid **24a** into indole-based heterocycles **27**–**29**.

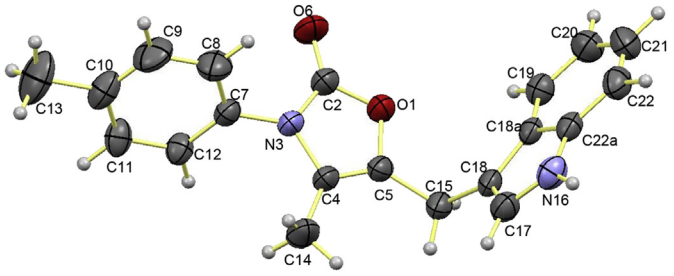


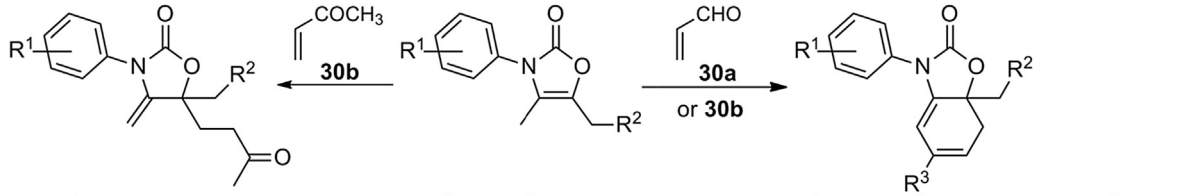
Fig. 2. X-ray structure of bis-heterocycle **27a** (ellipsoids with 30% probability).

When **24a** was herein submitted to identical conditions, the bis-heterocycle **28a** was generated in good yield (Scheme 7). This method was extended to pyrrole **15d** (Scheme 3), which reacts with dimethyl malonate to afford **28b** in 60% yield (see Experimental section).

2.4. Functionalization of 4-oxazolin-2-ones 10c, 10f, 17a, 22c, 22e, and 27b

The *N*-alkyl and *N*-aryl 4-oxazolin-2-one units have proven to be efficient regioselective nucleophilic agents, resulting in an exclusively C-5 attack on α,β-unsaturated carbonyl compounds such as acrolein (**30a**) and methyl vinyl ketone (**30b**).[5] However, at the C-4 and C-5 centers the 4-oxazolin-2-ones were only substituted by methyl groups. Since the herein prepared 4-oxazolin-2-ones are substituted at the C-5 center by a more complex and hindered group, they should be a good model for testing both the reactivity and selectivity with similar electrophilic species. We selected 4-oxazolin-2-ones **10c**, **10f**, **17a**, **22c**, **22e**, and **27b** as representative substrates for carrying out additions to conjugated carbonyl groups **30a**,**b** under similar thermal- and MW-assisted reaction conditions as previously described (Schemes 7 and 8).[5b]

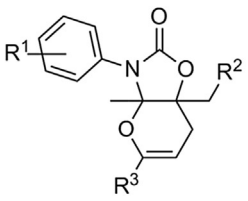
With severe thermal conditions (160 °C, 72 h), 4-oxazolin-2-ones **10c** and **17a** afforded the corresponding conjugated adducts **31a** and **31c**, respectively, by reacting with methyl vinyl ketone (**30b**) (Table 4, entries 1 and 3). The reaction time was shortened when MW irradiation was used with **10f** and **22e** to give adducts **31b** and **31d**, respectively (entries 2 and 4). It is noteworthy that, in contrast to 4,5-dimethyl-4-oxazolin-2-one,[5b] no diene like **32** was observed in any of these assays. Similar results were obtained even when adding methyl iodide, which is known to promote the formation of this type of diene.[5b] Finally, with reduced MW potency, the fused-cyclohexadiene oxazolidin-2-one **32a** was afforded in low yield upon mixing the substrate **10f** with acrolein (**30a**) (entry 5). The difficulty in achieving the latter cascade reaction (the 1,4-conjugated addition followed by the C–C bond formation via



31a, R^1 = H, R^2 = C_6H_2-2,4,5-OMe
31b, R^1 = 4-Cl, R^2 = C_6H_4-4-OMe
31c, R^1 = H, R^2 = 2-furanyl
31d, R^1 = 4-Me, R^2 = SC_6H_4-4-Cl

10c, R^1 = H, R^2 = C_6H_2-2,4,5-OMe
10f, R^1 = 4-Cl, R^2 = C_6H_4-4-OMe
17a, R^1 = H, R^2 = 2-furanyl
22c, R^1 = 4-Me, R^2 = SC_6H_4-3-Me
22e, R^1 = 4-Me, R^2 = SC_6H_4-4-Cl

32a, R^1 = 4-Cl, R^2 = C_6H_4-4-OMe, R^3 = H
32b, R^1 = 4-Cl, R^2 = C_6H_4-4-OMe, R^3 = Me



33a, R^1 = 4-Me, R^2 = SC_6H_4-3-Me, R^3 = H
33b, R^1 = 4-Cl, R^2 = C_6H_4-4-OMe, R^3 = Me

Scheme 8. Functionalization of 4-oxazolin-2-ones **10c**, **10f**, **17a**, **22c**, and **22e**.

Table 4
Preparation of derivatives **31**–**33** from the addition of 4-oxazolin-2-ones **10c**, **10f**, **17a**, **22c**, and **22e** to **30a**,**b**.[a]

Entry	4-Oxazolin-2-one	**30** (mol equiv)	MW (W)	T (°C)	t (h)	Product	Yield[b] (%)
1	**10c**	**30b** (5.0)	—	160	72	**31a**	68
2	**10f**	**30b** (4.0)	120	120	12	**31b**	82
3	**17a**	**30b** (5.0)	—	160	72	**31c**	78
4	**22e**	**30b** (4.0)	200	100	16	**31d**	65
5	**10f**	**30a** (5.0)	100	100	18	**32a**	38
6	**22c**	**30a** (10.0)	200	100	6	**33a**	78
7	**10f**	**30b** (5.0)	100	100	18	**33b**	70

[a] All under N_2 atmosphere, with 1.0 mol equiv of 4-oxazolin-2-one, and in the dark for the thermal trials.
[b] After column chromatography.

a cyclization process) is evidenced by the fact that the analogue compound **32b** was not obtained, the preference being for the C–O bond formation to afford the dihydropyrane **33a**. Morever, the reaction of **10f** with **30b** provided the fused dihydropyran **33b** rather than the desired diene **32b** (entry 7). This is probably because the dihydropyran is stable under mild reaction conditions, while severe conditions promote the opening of the heterocycle to form the observed conjugated addition product **31b**, or eventually the diene **32b**, which seems to be the thermodynamic product. An analogous result was observed by reacting **22c** with **30a** to provide dihydropyran **33a** in good yield (entry 6). Similarly, the reaction between 4-oxazolin-2-one **27b** with **30a** afforded the dihydropyran **29** (Scheme 7). These results agree with those found for the 4,5-dimethyl-4-oxazolin-2-ones, in which acrolein (**30a**) gives the respective fused dihydropyran rather than the addition product.[5b]

In summary, these results indicate that the C-5 substituted 4-oxazolin-2-ones **10c**, **10f**, **17a**, **22c**, **22e**, and **27b**, which bear the most hindered aryl-, heterocyclic-, and thio-methyl groups, show a decrease in reactivity towards the conjugated 1,4-addition to enones, even though regioselectivity at the C-5 center remained. The higher reactivity of these compounds suggests that the electron-donating effect of the nitrogen atom prevailed in spite of the steric hindrance generated by the substituent at this center.

3. Conclusions

The present results demonstrate a significant broadening of the previously reported approach for generating α-ketols **4** via Diels–Alder cycloadditions of the captodative alkenes **1**.[12,13] Through Lewis acid-promoted Friedel–Crafts reactions high reactivity was observed for captodative alkene **1a** with substituted benzene rings and heterocycles such as furan (**12a**), thiophene (**12b**), pyrrole (**12d**) and indole (**23a**). The adducts obtained were hydrolyzed to α-ketols, which were employed as the key building blocks for the construction of 4-oxazolin-2-ones and butenolides. Among the α-ketols prepared was naturally occurring alkaloid actinopolymorphol B (**24a**), synthesized in only two steps and in high overall yield, and a series of 1,3-disubstituted indole derivatives **24b-d**. With **24a** as starting material, the first total synthesis of natural alkaloid tanakine (**25**) was achieved, along with that of polycyclic derivatives **27**–**29**. A series of 4-oxazolin-2-ones was evaluated as a nucleophilic species in conjugated additions to enones **30a**,**b**, providing the corresponding 1,4-adducts **31a**–**d**, the cyclohexadiene- **32a**, or the dihydropyran-fused polycyclic derivatives **33a**,**b**. The selectivity of these reactions depended on whether the reaction conditions were thermal- or the MW-assisted. The present results show that in spite of the presence of hindered substituents at the C-5 heterocyclic center, the enamide π system of the 4-oxazolin-2-ones is controlling the activation of this center in the regioselective electrophilic addition. Moreover, due to the structural resemblance of the series of α-hydroxy ketones **7a**–**c**, **15a**–**d**, **16a**,**b**, **21a**–**e** and **24a**–**d** with the naturally occurring and highly biologically active α-hydroxy ketones kurasoins,[22c,23a] sattabacins[22a] and sattazolins,[22a,23a] the methodology herein developed may be a useful synthetic tool for the design of novel pharmacologically active agents. Therefore, these results improve the synthetic potential not only of alkene **1a**, but also of the diverse α-ketols prepared as precursors in a divergent approach for constructing novel heterocycles and natural products.

4. Experimental section

4.1. General methods

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin–Elmer 2000 spectrophotometer. ^{1}H (300 or 500 MHz) and ^{13}C (75 or 125 MHz) NMR spectra were recorded on Varian Mercury-300 and Varian VNMR System instruments, with TMS as internal standard; chemical shifts (δ) are reported in parts per million (ppm). Mass spectra were recorded on Polaris Q-Trace GC Ultra (Finnigan Co.) and Hewlett–Packard 5971A spectrometers. High-resolution mass spectra (HRMS), in electron impact mode, were obtained with a Jeol JSM-GCMateII apparatus. Elemental analyses were performed on a CE-440 Exeter Analytical instrument. X-ray crystallographic measurements were collected on an Oxford XcaliburS diffractometer with Mo Kα radiation (graphite crystal monochromator, λ=0.7107 Å). Microwave (MW) irradiation was performed with SEV/MIC-1 (Mexico)[26] and CEM MW reactors. Analytical thin-layer chromatography was carried out using E. Merck silica gel 60 F_{254} coated 0.25 plates, visualized by using a long- and short-wavelength UV lamp. Flash column chromatography was performed over Natland International Co. silica gel (230–400 mesh). All air moisture sensitive reactions were carried out under nitrogen using oven-dried glassware. THF was freshly distilled from sodium prior to use, as was methylene chloride from calcium hydride. Triethylamine was freshly distilled from NaOH. All other reagents were used without further purification. Toluene, MeOH, and MeCN were freshly distilled over sodium prior to use, as was DMF over calcium hydride. Acetone was dried by distillation after treatment with potassium permanganate. K_2CO_3 and Li_2CO_3 were dried overnight at 200 °C prior to use. All other reagents were used without further purification. Compound **1a**,[5d] the series of adducts **6a**–**c**, and α-ketols **7a**,**b**[15] were prepared as previously described.

4.2. General procedure for the preparation of 13a–d and 14a,b

To a solution of **1a** (1.0 mol equiv) in dry CH_2Cl_2 (8 mL), at 0 °C, the Lewis acid (0.05–20.0 mol equiv) and the nucleophile (0.5–10.0 mol equiv) were successively added. The mixture was stirred at 10–25 °C under nitrogen for 2–120 h. EtOAc (75 mL) was added, and the mixture was washed with water (2×10 mL), a saturated aqueous solution of $NaHCO_3$ (3×15 mL), and again water until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 9:1) to give the desired products **13a**–**d** and **14a**,**b**.

*4.2.1. 1-(Furan-2-yl)-3-oxobutan-2-yl 4-nitrobenzoate (**13a**).* According to the general procedure, by using **1a** (0.500 g, 2.13 mmol), **12a** (1.45 g, 21.3 mmol), and $AlCl_3$ (0.142 g, 1.06 mmol) and after stirring at 25 °C for 8 h, **13a** (0.477 g, 74%) was obtained as a pale yellow solid: R_f 0.56 (hexane/EtOAc, 7:3); mp 75–77 °C. IR (film): $\bar{\nu}$=1726, 1530, 1349, 1104, 844, 738, 716 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.21 (s, 3H, CH_3CO), 3.27–3.37 (m, 2H, H-1′), 5.54 (dd, J=7.0, 5.5 Hz, 1H, H-2′), 6.17 (br d, J=2.5 Hz, 1H, H-3″), 6.31

(dd, J=2.5, 1.5 Hz, 1H, H-4″), 7.34 (d, J=1.5 Hz, 1H, H-5″), 8.19–8.22 (m, 2H, H-2), 8.28–8.31 (m, 2H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ=26.6 (*C*H$_3$CO), 29.3 (C-1′), 77.8 (C-2′), 108.1 (C-3″), 110.5 (C-4″), 123.6 (C-3), 130.9 (C-2), 134.5 (C-1), 142.2 (C-5″), 149.2 (C-2″), 150.8 (C-4), 163.9 (Ar*C*O$_2$), 203.5 (CH$_3$*C*O). MS (70 eV): m/z (%)=303 (1) [M]$^+$, 150 (41), 136 (39), 121 (30), 94 (100). Anal. Calcd for $C_{15}H_{13}NO_6$: C, 59.41; H, 4.32; N, 4.62. Found: C, 59.37; H, 4.28; N, 4.64.

*4.2.2. 3-Oxo-1-(thiophen-2-yl)butan-2-yl 4-nitrobenzoate (**13b**).* According to the general procedure, by using **1a** (0.200 g, 0.85 mmol), **12b** (0.714 g, 8.50 mmol), and $BF_3\cdot Et_2O$ (0.578 g, 4.10 mmol) and after stirring at 25 °C for 5 h, **13b** (0.231 g, 85%) was obtained as a pale yellow solid: R_f 0.70 (hexane/EtOAc, 7:3); mp 92–93 °C. IR (film): $\overline{\nu}$=1725, 1605, 1528, 1349, 1098 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.20 (s, 3H, C*H*$_3$CO), 3.47–3.51 (m, 2H, H-1′), 5.49 (dd, J=6.5, 5.3 Hz, 1H, H-2′), 6.91 (br d, J=3.5 Hz, 1H, H-3″), 6.95 (dd, J=5.1, 3.5 Hz, 1H, H-4″), 7.21 (dd, J=5.1, 1.3 Hz, 1H, H-5″), 8.22–8.37 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.9 (*C*H$_3$CO), 30.9 (C-1′), 79.6 (C-2′), 123.6 (C-3), 125.1 (C-5″), 126.9 (C-3″ or C-4″), 127.0 (C-4″ or C-3″), 131.0 (C-2), 134.4 (C-1), 136.7 (C-2″), 150.8 (C-4), 163.9 (Ar*C*O$_2$), 203.6 (CH$_3$*C*O). MS (70 eV): m/z (%)=152 (M$^+$−167, 48), 150 (39), 137 (85), 104 (62), 97 (100), 76 (66). Anal. Calcd for $C_{15}H_{13}NO_5S$: C, 56.42; H, 4.10; N, 4.38. Found: C, 56.55; H, 4.46; N, 4.33.

*4.2.3. 1-(5-Chlorothiophen-2-yl)-3-oxobutan-2-yl 4-nitrobenzoate (**13c**).* According to the general procedure, by using **1a** (0.050 g, 0.21 mmol), **12c** (0.250 g, 2.10 mmol), and $BF_3\cdot Et_2O$ (0.148 g, 1.05 mmol) in dry CH_2Cl_2 (5 mL) and after stirring at 25 °C for 6 h, **13c** (0.052 g, 68%) was obtained as a pale yellow solid: R_f 0.75 (hexane/EtOAc, 7:3); mp 91–92 °C. IR (film): $\overline{\nu}$=1728, 1530, 1350, 1103 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.22 (s, 3H, C*H*$_3$CO), 3.38–3.41 (m, 2H, H-1′), 5.47 (dd, J=6.1, 5.5 Hz, 1H, H-2′), 6.70 (br d, J=3.7 Hz, 1H, H-3″), 6.75 (d, J=3.7 Hz, 1H, H-4″), 8.23–8.37 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.9 (*C*H$_3$CO), 31.4 (C-1′), 79.2 (C-2′), 123.8 (C-3), 126.0 (C-3″ or C-4″), 126.4 (C-4″ or C-3″), 129.2 (C-5), 131.0 (C-2), 134.3 (C-1), 135.6 (C-2″), 150.1 (C-4), 163.9 (Ar*C*O$_2$), 203.3 (CH$_3$*C*O). MS (70 eV): m/z (%)=186 (M$^+$−167, 88), 173 (16), 171 (44), 151 (100), 150 (60), 133 (32), 131 (74), 104 (39), 76 (26). Anal. Calcd for $C_{15}H_{12}ClNO_5S$: C, 50.93; H, 3.42; N, 3.95. Found: C, 50.67; H, 3.40; N, 3.69.

*4.2.4. 3-Oxo-1-(1H-pyrrol-2-yl)butan-2-yl 4-nitrobenzoate (**13d**).* According to the general procedure, by using **1a** (0.100 g, 0.426 mmol), **12d** (0.114 g, 1.70 mmol), and I_2 (0.005 g, 0.021 mmol) in dry CH_2Cl_2 (5 mL) and after stirring at 25 °C for 5 h, the mixture was washed with an aqueous saturated solution of sodium hydrosulfite until neutral, and then dried with Na_2SO_4. The solvent was removed under vacuum and the product purified by column chromatography in order to obtain **13d** (0.062 g, 48%) as a pale yellow solid: R_f 0.40 (hexane/EtOAc, 7:3); mp 113–115 °C. IR (film): $\overline{\nu}$=3457, 1720, 1606, 1525, 1349, 1287, 1237, 1114, 878, 738, 719 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.16 (s, 3H, C*H*$_3$CO), 3.28 (d, J=5.7 Hz, 2H, H-1′), 5.48 (t, J=5.7 Hz, 1H, H-2′), 6.01–6.08 (m, 1H, H-3″), 6.13 (dd, J=5.9, 2.7 Hz, 1H, H-4″), 6.69–6.75 (m, 1H, H- 5″), 8.19–8.25 (m, 2H, H-2), 8.30–8.35 (m, 2H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=27.0 (*C*H$_3$CO), 29.1 (C-1′), 79.1 (C-2′), 108.0 (C-3″), 108.8 (C-4″), 117.8 (C-5″), 123.8 (C-3), 124.9 (C-2″), 130.9 (C-2), 134.5 (C-1), 151.0 (C-4), 164.0 (Ar*C*O$_2$), 205.1 (CH$_3$*C*O). MS (70 eV): m/z (%)=302 (M$^+$, 1), 150 (19), 135 (100), 134 (55), 120 (37), 80 (24). Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.64; H, 4.67; N, 9.23.

*4.2.5. Furan-2,5-diylbis(3-oxobutane-2,1-diyl) bis(4-nitrobenzoate) (**14a**).* According to the general procedure, by using **1a** (0.434 g, 1.85 mmol), **12a** (0.063 g, 0.93 mmol), and $BF_3\cdot Et_2O$ (0.578 g, 4.10 mmol) and after stirring at 25 °C for 2 h, **14a** (0.397 g, 80%) was obtained as a pale yellow solid: R_f 0.15 (hexane/EtOAc, 7:3); mp 112–114 °C. IR (film): $\overline{\nu}$=1726, 1530, 1349, 1104 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.19 (s, 3H, C*H*$_3$CO), 2.20 (s, 3H, C*H*$_3$CO), 3.19–3.29 (m, 4H, 2H-1′), 5.49 (t, J=5.2 Hz, 1H, H-2′), 5.50 (t, J=5.2 Hz, 1H, H-2′), 6.08 (s, 2H, H-3″, H-4″), 8.16–8.21 (m, 4H, ArH), 8.25–8.30 (m, 4H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=26.6 (*C*H$_3$CO), 29.4 (C-1′), 77.65 (C-2′), 77.69 (C-2′), 109.2 (C-3″, C-4″), 123.6 (C-3), 130.9 (C-2), 134.4 (C-1), 149.0 (C-2″, C-5″), 150.8 (C-4), 163.8 (Ar*C*O$_2$), 203.2 (CH$_3$*C*O). Anal. Calcd for $C_{26}H_{22}N_2O_{11}$: C, 58.02; H, 4.09; N, 5.20. Found: C, 58.07; H, 4.04; N, 5.13.

*4.2.6. Thiophene-2,5-diylbis(3-oxobutane-2,1-diyl) bis(4-nitrobenzoate) (**14b**).* According to the general procedure, by using **1a** (0.235 g, 1.00 mmol), **12b** (0.160 g, 0.50 mmol), and $BF_3\cdot Et_2O$ (0.578 g, 4.10 mmol) and after stirring at 25 °C for 120 h, **14b** (0.208 g, 75%) was obtained as a pale yellow solid: R_f 0.38 (hexane/EtOAc, 7:3); mp 182–184 °C. IR (film): $\overline{\nu}$=1732, 1726, 1526, 1344, 1273, 1097 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.16 (s, 3H, C*H*$_3$CO), 2.18 (s, 3H, C*H*$_3$CO), 3.41–3.45 (m, 4H, 2H-1′), 5.44–5.51 (m, 2H, 2H-2′), 6.72 (br s, 2H, H-3″, H-4″), 8.12–8.32 (m, 8H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.9 (*C*H$_3$CO), 31.2 (C-1′), 79.3 (C-2′), 79.4 (C-2′), 123.7 (C-3), 127.0 (C-3″, C-4″), 130.9 (C-2), 134.3 (C-1), 134.3 (C-2″, C-5″), 150.8 (C-4), 163.8 (Ar*C*O$_2$), 203.3 (CH$_3$*C*O). Anal. Calcd for $C_{26}H_{22}N_2O_{12}S$: C, 56.31; H, 3.99; N, 5.05. Found: C, 56.40; H, 4.25; N, 5.21.

4.3. General procedure for the preparation of 20a–e

A mixture of **19** (1.1 mol equiv) with DMAP (0.4 mol equiv) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 10 min, and then **1a** (1.0 mol equiv) was added, and stirred at the same temperature under nitrogen for 2–3 h. Then, the mixture was washed with water (2×20 mL) and with a 5% aqueous solution of HCl until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 9:1) to give the desired products **20a–e**.

*4.3.1. 3-Oxo-1-(phenylthio)butan-2-yl 4-nitrobenzoate (**20a**).* According to the general procedure, by using **1a** (0.100 g, 0.426 mmol), **19a** (0.051 g, 0.464 mmol), and DMAP (0.021 g, 0.17 mmol) and after stirring at room temperature for 2 h, **20a** (0.135 g, 92%) was obtained as a yellow solid: R_f 0.58 (hexane/EtOAc, 7:3); mp 84–85 °C. IR (film): $\overline{\nu}$=1720, 1524, 1346, 1266, 1101, 845, 746, 717 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.28 (s, 3H, C*H*$_3$CO), 3.42 (dd, J=14.7, 7.2 Hz, 1H, H-1′), 3.55 (dd, J=14.7, 7.2 Hz, 1H, H-1′), 5.47 (dd, J=7.2, 4.1 Hz, 1H, H-2′), 7.21–7.33 (m, 3H, H-3″, H-4″), 7.41–7.46 (m, 2H, H-2″), 7.94–7.95 (m, 2H, H-2), 8.20–8.25 (m, 2H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=27.1 (*C*H$_3$CO), 34.9 (C-1′), 78.9 (C-2′), 123.5 (C-3), 127.2 (C-4″), 129.3 (C-3″), 131.0 (C-2), 134.1 (C-1), 134.6 (C-1″), 150.7 (C-4), 163.9 (Ar*C*O$_2$), 203.0 (CH$_3$*C*O). MS (70 eV): m/z (%)=345 (M$^+$, 1), 303 (4), 252 (3), 224 (7), 160 (5), 138 (7), 105 (5), 88 (100), 57 (23). HRMS (EI) m/z [M$^+$] calcd for $C_{17}H_{15}NO_5S$: 345.0671. Found: 345.0672.

*4.3.2. 3-Oxo-1-(m-tolylthio)butan-2-yl 4-nitrobenzoate (**20b**).* According to the general procedure, by using **1a** (0.100 g, 0.426 mmol), **19b** (0.058 g, 0.468 mmol), and DMAP (0.021 g, 0.17 mmol) and after stirring at room temperature for 3 h, **20b** (0.146 g, 95%) was obtained as a yellow oil: R_f 0.44 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=1721, 1592, 1524, 1474, 1345, 1264, 1163, 1100, 1013, 844, 776, 716 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.27 (s, 3H, Ar−C*H*$_3$), 2.28 (s, 3H, C*H*$_3$CO), 3.41 (dd, J=14.7, 7.5 Hz, 1H, H-1′), 3.53 (dd, J=14.7, 4.2 Hz, 1H, H-1′), 5.47 (dd, J=7.5, 4.2 Hz, 1H, H-2′), 7.03 (br d, J=7.5 Hz, 1H, H-4″), 7.14–7.25 (m, 3H, H-2″, H-5″, H-6″), 7.93–8.00 (m, 2H, H-2), 8.18–8.25 (m, 2H, H-3). ^{13}C NMR (75 MHz,

$CDCl_3$): δ=21.2 (Ar–CH_3), 27.1 (CH_3CO), 34.8 (C-1′), 79.0 (C-2′), 123.4 (C-3), 127.8 (C-6″), 128.0 (C-4″), 129.1 (C-2″), 130.9 (C-2), 131.4 (C-5″), 134.1 (C-1), 134.3 (C-1″), 139.1 (C-3″), 150.6 (C-4), 163.8 ($ArCO_2$), 203.0 (CH_3CO). MS (70 eV): *m*/*z* (%)=359 (M^+, 1), 193 (20), 192 (100), 177 (44), 150 (41), 149 (80), 92 (14). HRMS (EI) *m*/*z* [M^+] calcd for $C_{18}H_{17}NO_5S$: 359.0827. Found: 359.0824.

*4.3.3. 1-((3-Methoxyphenyl)thio)-3-oxobutan-2-yl 4-nitrobenzoate (**20c**).* According to the general procedure, by using **1a** (0.100 g, 0.426 mmol), **19c** (0.065 g, 0.464 mmol), and DMAP (0.021 g, 0.17 mmol) and after stirring at room temperature for 3 h, **20c** (0.147 g, 92%) was obtained as a yellow oil: R_f 0.60 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$=1720, 1588, 1524, 1477, 1346, 1266, 1100, 1037, 844, 769, 717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.29 (s, 3H, CH_3CO), 3.42 (dd, *J*=14.7, 7.1 Hz, 1H, H-1′), 3.55 (dd, *J*=14.7, 3.9 Hz, 1H, H-1′), 3.75 (s, 3H, CH_3O), 5.49 (dd, *J*=7.1, 3.9 Hz, 1H, H-2′), 6.74 (ddd, *J*=7.8, 2.4, 0.9 Hz, 1H, H-4″), 6.95 (t, *J*=2.4 Hz, 1H, H-2″), 6.99 (ddd, *J*=7.8, 1.5, 0.9 Hz, 1H, H-6″), 7.19 (t, *J*=7.8 Hz, 1H, H-5″), 7.94–8.03 (m, 2H, H-2), 8.19–8.25 (m, 2H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=27.1 (CH_3CO), 34.6 (C-1′), 55.2 (OCH_3), 78.9 (C-2′), 112.6 (C-4″), 116.1 (C-2″), 122.6 (C-6″), 123.4 (C-3), 130.0 (C-5″), 131.0 (C-2), 134.1 (C-1), 135.8 (C-1″), 150.6 (C-4), 159.9 (C-3″), 163.8 ($ArCO_2$), 203.0 (CH_3CO). HRMS (EI) *m*/*z* [M^+] calcd for $C_{18}H_{17}NO_6S$: 375.0777. Found: 375.0779.

*4.3.4. 1-((4-Chlorophenyl)thio)-3-oxobutan-2-yl 4-nitrobenzoate (**20d**).* According to the general procedure, by using **1a** (0.100 g, 0.426 mmol), **19d** (0.067 g, 0.464 mmol), and DMAP (0.021 g, 0.17 mmol) and after stirring at room temperature for 3 h, **20d** (0.145 g, 90%) was obtained as a yellow solid: R_f 0.44 (hexane/EtOAc, 7:3); mp 94–96 °C. IR (film): $\bar{\nu}$=1722, 1606, 1524, 1475, 1410, 1347, 1265, 1163, 1095, 1012, 871, 845, 816, 717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.29 (s, 3H, CH_3CO), 3.40 (dd, *J*=14.7, 7.2 Hz, 1H, H-1′), 3.53 (dd, *J*=14.7, 3.9 Hz, 1H, H-1′), 5.49 (dd, *J*=7.2, 3.9 Hz, 1H, H-2′), 7.20–7.26 (m, 2H, H-2″), 7.33–7.38 (m, 2H, H-3″), 7.95–8.00 (m, 2H, H-2), 8.24–8.29 (m, 2H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=27.1 (CH_3CO), 35.1 (C-1′), 78.8 (C-2′), 123.5 (C-3), 129.4 (C-2″), 130.9 (C-2), 132.4 (C-3″), 133.1 (C-4″), 133.4 (C-1″), 133.9 (C-1), 150.8 (C-4), 163.8 ($ArCO_2$), 202.8 (CH_3CO). MS (70 eV): *m*/*z* (%)=379 (M^+, 1), 212 (100), 150 (31), 92 (19). HRMS (EI) *m*/*z* [M^+] calcd for $C_{17}H_{14}NO_5SCl$: 379.0281. Found: 379.0278.

*4.3.5. 1-((2-Bromophenyl)thio)-3-oxobutan-2-yl 4-nitrobenzoate (**20e**).* According to the general procedure, by using **1a** (0.100 g, 0.426 mmol), **19e** (0.065 g, 0.464 mmol), and DMAP (0.021 g, 0.17 mmol) and after stirring at room temperature for 3 h, **20e** (0.144 g, 80%) was obtained as a yellow solid: R_f 0.32 (hexane/EtOAc, 7:3); mp 78–79 °C. IR (film): $\bar{\nu}$=1722, 1606, 1524, 1449, 1346, 1266, 1100, 1015, 871, 845, 748, 717 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=2.31 (s, 3H, CH_3CO), 3.45 (dd, *J*=14.5, 7.4 Hz, 1H, H-1′), 3.59 (dd, *J*=14.5, 4.0 Hz, 1H, H-1′), 5.49 (dd, *J*=7.4, 4.0 Hz, 1H, H-2′), 7.09 (td, *J*=7.8, 1.7 Hz, 1H, H-4″), 7.26 (td, *J*=7.8, 1.5 Hz, 1H, H-5″), 7.46 (dd, *J*=7.8, 1.7 Hz, 1H, H-6″), 7.56 (dd, *J*=7.8, 1.5 Hz, 1H, H-3″), 8.04–8.08 (m, 2H, H-2), 8.24–8.28 (m, 2H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ=27.1 (CH_3CO), 34.2 (C-1′), 78.5 (C-2′), 123.5 (C-3), 126.1 (C-2″), 128.0 (C-5″), 128.4 (C-4″), 131.0 (C-2), 131.5 (C-6″), 133.5 (C-3″), 134.0 (C-1), 135.5 (C-1″), 150.7 (C-4), 163.8 ($ArCO_2$), 202.9 (CH_3CO). MS (70 eV): *m*/*z* (%)=423 (M^+, 1), 253 (100), 251 (60), 235 (34), 233 (21), 150 (13), 79 (19). Anal. Calcd for $C_{17}H_{14}BrNO_5S$: C, 48.13; H, 3.33; N, 3.30. Found: C, 48.09; H, 3.28; N, 3.30.

4.4. General procedure for the preparation of 7c, 15a–d, and 16a,b

A mixture of **6c** or **13** or **14** (1.0 mol equiv) and K_2CO_3 (3.0–4.0 mol equiv) in THF/MeOH was stirred at room temperature for 10–90 min (see Table 2). Afterward, a saturated aqueous solution of NH_4Cl (30 mL) was added and then extracted with CH_2Cl_2 (4×25 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 9:1) to give the desired products **7c**, **15a–d**, and **16a,b**, respectively.

*4.4.1. 3-Hydroxy-4-(2,4,5-trimethoxyphenyl)butan-2-one (**7c**).* According to the general procedure, by using **6c** (0.20 g, 0.5 mmol) and K_2CO_3 (0.276 g, 2.00 mmol) in 20 mL of THF/MeOH (2:1), **7c** (0.116 g, 92%) was obtained as a yellow oil: R_f 0.54 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$=3477, 2936, 1710, 1609, 1514, 1461, 1400, 1355, 1314, 1204, 1119, 1085, 1033, 850 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.21 (s, 3H, CH_3CO), 2.89 (dd, *J*=14.1, 6.6 Hz, 1H, H-4), 3.05 (dd, *J*=14.1, 5.0 Hz, 1H, H-4), 3.47 (br d, *J*=5.4 Hz, 1H, OH), 3.79 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 4.38–4.45 (m, 1H, H-3), 6.51 (s, 1H, H-3′), 6.76 (s, 1H, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.6 (CH_3CO), 34.0 (C-4), 55.7 (CH_3O), 55.9 (CH_3O), 56.3 (CH_3O), 76.7 (C-3), 96.9 (C-3′), 115.3 (C-6′), 115.6 (C-1′), 142.5 (C-5′), 148.3 (C-4′), 151.1 (C-2′), 209.8 (CH_3CO). MS (70 eV): *m*/*z* (%)=254 (M^+, 18), 181 (40), 151 (100), 136 (48), 121 (23), 107 (30), 91 (58), 79 (58), 77 (48), 43 (43). HRMS (FAB^+) *m*/*z* [M^+] calcd for $C_{13}H_{18}O_5$: 254.1154. Found: 254.1160.

*4.4.2. 4-(Furan-2-yl)-3-hydroxybutan-2-one (**15a**).* According to the general procedure, by using **13a** (1.00 g, 3.3 mmol) and K_2CO_3 (1.37 g, 9.9 mmol) in 40 mL of THF/MeOH (1:1), **15a** (0.44 g, 86%) was obtained as a yellow oil: R_f 0.32 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$=3365, 3100, 1713, 1354, 1155, 1090, 1008 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=2.22 (s, 3H, CH_3CO), 3.05 (dd, *J*=15.5, 6.0 Hz, 1H, H-4), 3.14 (dd, *J*=15.5, 5.0 Hz, 1H, H-4), 3.59 (br d, *J*=5.5 Hz, 1H, OH), 4.41 (q, *J*=5.5 Hz, 1H, H-3), 6.13 (br d, *J*=3.0 Hz, 1H, H-3′), 6.29 (dd, *J*=3.0, 1.5 Hz, 1H, H-4′), 7.31 (d, *J*=1.5 Hz, 1H, H-5′). ^{13}C NMR (125 MHz, $CDCl_3$): δ=25.4 (CH_3CO), 32.4 (C-4), 75.4 (C-3), 107.8 (C-3′), 110.4 (C-4′), 141.7 (C-5′), 150.2 (C-2′), 208.7 (CH_3CO). MS (70 eV): *m*/*z* (%)=154 (M^+, 1), 151 (22), 125 (13), 120 (24), 111 (6), 85 (16), 83 (16), 73 (100). HRMS (EI) *m*/*z* [M^+] calcd for $C_8H_{10}O_3$: 154.0630. Found: 154.0626.

*4.4.3. 3-Hydroxy-4-(thiophen-2-yl)butan-2-one (**15b**).* According to the general procedure, by using **13b** (0.89 g, 2.8 mmol) and K_2CO_3 (1.16 g, 8.4 mmol) in 40 mL of THF/MeOH (1:1), **15b** (0.45 g, 94%) was obtained as a pale yellow oil: R_f 0.31 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$=3455, 1712, 1440, 1350, 1182, 1081 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.21 (s, 3H, CH_3CO), 3.21 (dd, *J*=15.2, 5.9 Hz, 1H, H-4), 3.36 (ddd, *J*=15.2, 4.6, 0.9, Hz, 1H, H-4), 3.64 (br d, *J*=5.6 Hz, 1H, OH), 4.30–4.44 (m, 1H, H-3), 6.86–6.88 (m, 1H, H-3′), 6.96 (dd, *J*=5.1, 3.4 Hz, 1H, H-4′), 7.20 (dd, *J*=5.1, 1.2 Hz, 1H, H-5′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.6 (CH_3CO), 34.0 (C-4), 77.1 (C-3), 124.7 (C-5′), 126.4 (C-3′ or C-4′), 126.7 (C-4′ or C-3′), 137.5 (C-2′), 208.3 (CH_3CO). MS (70 eV): *m*/*z* (%)=170 (M^+, 4), 152 (25), 137 (10), 126 (2), 99 (34), 97 (100), 65 (8). HRMS (EI) *m*/*z* [M^+] calcd for $C_8H_{10}O_2S$: 170.0402. Found: 170.0408.

*4.4.4. 4-(5-Chlorothiophen-2-yl)-3-hydroxybutan-2-one (**15c**).* According to the general procedure, by using **13c** (1.50 g, 4.2 mmol) and K_2CO_3 (1.74 g, 12.6 mmol) in 40 mL of THF/MeOH (1:1), **15c** (0.78 g, 90%) was obtained as a pale yellow oil: R_f 0.52 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$=3466, 1714, 1447, 1354, 1272, 1256, 1087 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.20 (s, 3H, CH_3CO), 3.15 (ddd, *J*=16.8, 6.4, 0.6 Hz, 1H, H-4), 3.33 (ddd, *J*=16.8, 4.7, 1.1 Hz, 1H, H-4), 3.79 (br d, *J*=5.8 Hz, 1H, OH), 4.49–4.57 (m, 1H, H-3), 6.98 (dm, *J*=3.8 Hz, 1H, H-3′), 7.07 (d, *J*=3.8 Hz, 1H, H-4′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.4 (CH_3CO), 34.5 (C-4), 76.6 (C-3), 125.5 (C-3′ or C-4′), 125.6 (C-4′ or C-3′), 128.8 (C-5′), 136.4 (C-2′), 207.8 (CH_3CO). MS (70 eV): *m*/*z* (%)=206 (M^++2, 3), 204 (M^+, 7), 188 (6),

186 (17), 171 (4), 151 (6), 133 (45), 131 (100), 97 (25), 69 (7). HRMS (EI) m/z [M^+] calcd for $C_8H_9ClO_2S$: 204.0012. Found: 204.0007.

*4.4.5. 3-Hydroxy-4-(1H-pyrrol-2-yl)butan-2-one (**15d**).* According to the general procedure, by using **13d** (0.500 g, 1.66 mmol) and K_2CO_3 (0.685 g, 4.97 mmol) in 20 mL of THF/MeOH (1:1), **15d** (0.21 g, 84%) was obtained as a brown oil: R_f 0.20 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=3391, 2919, 1713, 1417, 1358, 1173, 1094, 1027, 792, 726 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=2.18 (s, 3H, CH_3CO), 2.93 (dd, J=15.0, 6.0 Hz, 1H, H-4), 3.14 (dd, J=15.0, 4.0 Hz, 1H, H-4), 3.84 (br s, 1H, OH), 4.33 (dd, J=6.0, 4.0 Hz, 1H, H-3), 5.92–5.93 (m, 1H, H-3′), 6.06–6.08 (m, 1H, H-4′), 6.64–6.66 (m, 1H, H-5′), 8.72 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=25.2 (CH_3CO), 31.3 (C-4), 77.0 (C-3), 106.6 (C-4′), 107.7 (C-3′), 117.6 (C-5′), 126.6 (C-2′), 208.8 (CH$_3$CO). MS (70 eV): m/z (%)=153 (M^+, 1), 120 (6), 92 (11), 80 (100), 73 (19), 53 (16). HRMS (EI) m/z [M^+] calcd for $C_8H_{11}NO_2$: 153.0790. Found: 153.0792.

*4.4.6. 4,4′-(Furan-2,5-diyl)bis(3-hydroxybutan-2-one) (**16a**).* According to the general procedure, by using **14a** (0.400 g, 0.74 mmol) and K_2CO_3 (0.408 g, 2.96 mmol) in 20 mL of THF/MeOH (1:1), **16a** (0.152 g, 85%) was obtained as a brown oil: R_f 0.22 (EtOAc). IR (film): $\overline{\nu}$=3429, 1709, 1418, 1357, 1245, 1160, 1086, 1016, 967, 790 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.23 (s, 3H, CH_3CO), 2.25 (s, 3H, CH_3CO′), 2.96–3.15 (m, 4H, 2H-4), 3.48–3.56 (br s, 2H, 2OH), 4.37–4.43 (m, 2H, 2H-3), 6.04 (br s, 2H, H-3″, H-4″). ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.56 (CH_3CO), 25.58 (CH_3CO′), 32.45 (C-4), 32.45 (C-4′), 75.40 (C-3), 75.44 (C-3′), 108.83 (C-3″), 108.88 (C-4″), 149.5 (C-2″, C-5″), 208.83 (CH$_3$CO), 208.86 (CH$_3$CO′). MS (70 eV): m/z (%)=241 (M^++1, 0.2), 223 (1), 205 (1), 149 (39), 121 (67), 95 (33), 67 (31), 55 (33), 43 (100). HRMS (EI) m/z [M^+] calcd for $C_{12}H_{16}O_5$: 240.0998. Found: 240.0989.

*4.4.7. 4,4′-(Thiophene-2,5-diyl)bis(3-hydroxybutan-2-one) (**16b**).* According to the general procedure, by using **14b** (0.300 g, 0.54 mmol) and K_2CO_3 (0.298 g, 2.16 mmol) in 20 mL of THF/MeOH (1:1), **16b** (0.113 g, 82%) was obtained as a pale yellow solid: R_f 0.24 (EtOAc); mp 85–86 °C. IR (film): $\overline{\nu}$=3433, 1710, 1662, 1354, 1272, 1083, 970, 796 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.21 (s, 3H, CH_3CO), 2.22 (s, 3H, CH_3CO′), 3.12 (dd, J=15.3, 6.0 Hz, 2H, H-4, H-4′), 3.29 (dd, J=15.3, 4.5 Hz, 2H, H-4, H-4′), 3.63 (br d, J=5.0 Hz, 2H, 2OH), 4.36–4.43 (m, 2H, 2H-3), 6.69 (d, J=2.8 Hz, 2H, H-3″, H-4″). ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.6 (2CH_3CO), 34.18 (C-4), 34.23 (C-4′), 76.9 (C-3, C-3′), 126.05 (C-3″), 126.14 (C-4″), 136.97 (C-2″), 137.08 (C-5″), 208.4 (2CH$_3$CO). MS (70 eV): m/z (%)=256 (M^+, 0.2), 239 (0.5), 183 (22), 165 (94), 137 (78), 111 (71), 97 (26), 77 (41), 67 (27), 45 (60), 43 (100). Anal. Calcd for $C_{12}H_{16}SO_4$: C, 56.23; H, 6.29. Found: C, 56.40; H, 6.45.

4.5. General procedure for the preparation of 21a–e

A mixture of **20** (1.0 mol equiv) and Li_2CO_3 (2.0 mol equiv) in DMF/MeOH (1:1) was stirred at room temperature for 24 h. Afterward a saturated aqueous solution of NH_4Cl (30 mL) was added and then extracted with CH_2Cl_2 (4×25 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 95:5) to give the desired products **21a**–**e**.

*4.5.1. 3-Hydroxy-4-(phenylthio)butan-2-one (**21a**).* According to the general procedure, by using **20a** (0.900 g, 2.61 mmol) and Li_2CO_3 (0.385 g, 5.20 mmol) in 30 mL of DMF/MeOH (1:1), **21a** (0.44 g, 85%) was obtained as a yellow oil: R_f 0.29 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=3445, 1716, 1582, 1480, 1438, 1356, 1278, 1164, 1088, 742, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.19 (s, 3H, CH_3CO), 3.16 (dd, J=14.1, 6.3 Hz, 1H, H-4), 3.42 (dd, J=14.1, 4.4 Hz, 1H, H-4), 3.68 (br d, J=4.8 Hz, 1H, OH), 4.28–4.35 (m, 1H, H-3), 7.20–7.27 (m, 1H, H-4′), 7.27–7.34 (m, 2H, H-3′), 7.39–7.44 (m, 2H, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.8 (CH_3CO), 38.4 (C-4), 75.4 (C-3), 127.0 (C-4′), 129.1 (C-3′), 130.6 (C-2′), 134.7 (C-1′), 207.8 (CH$_3$CO). MS (70 eV): m/z (%)=197 (M^++1, 2), 179 (12), 137 (15), 133 (51), 117 (17), 87 (32), 85 (100). HRMS (EI) m/z [M^+] calcd for $C_{10}H_{12}O_2S$: 196.0558. Found: 196.0557.

*4.5.2. 3-Hydroxy-4-(m-tolylthio)butan-2-one (**21b**).* According to the general procedure, by using **20b** (0.693 g, 1.93 mmol) and Li_2CO_3 (0.286 g, 3.86 mmol) in 30 mL of DMF/MeOH (1:1), **21b** (0.35 g, 86%) was obtained as a yellow oil: R_f 0.55 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=3442, 1716, 1592, 1574, 1475, 1416, 1356, 1277, 1165, 1084, 855, 774, 689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.19 (s, 3H, CH_3CO), 2.32 (s, 3H, ArCH$_3$), 3.15 (dd, J=14.0, 6.0 Hz, 1H, H-4), 3.40 (dd, J=14.0, 4.4 Hz, 1H, H-4), 3.72 (br s, 1H, OH), 4.30 (dd, J=6.0, 4.4 Hz, 1H, H-3), 7.01–7.06 (m, 1H, H-4′), 7.15–7.24 (m, 3H, H-2′, H-5′, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.2 (s, 3H, ArCH$_3$), 25.7 (CH_3CO), 38.3 (C-4), 75.4 (C-3), 127.4 (C-6′), 127.8 (C-4′), 128.9 (C-2′), 131.1 (C-5′), 134.4 (C-1′), 138.9 (C-3′), 208.0 (CH$_3$CO). MS (70 eV): m/z (%)=210 (M^+, 1), 191 (62), 183 (63), 163 (60), 155 (62), 149 (100), 139 (89), 124 (52), 119 (37), 91 (91). HRMS (EI) m/z [M^+] calcd for $C_{11}H_{14}O_2S$: 210.0715. Found: 210.0717.

*4.5.3. 3-Hydroxy-4-((3-methoxyphenyl)thio)butan-2-one (**21c**).* According to the general procedure, by using **20c** (0.600 g, 1.60 mmol) and Li_2CO_3 (0.237 g, 3.20 mmol) in 30 mL of DMF/MeOH (1:1), **21c** (0.30 g, 83%) was obtained as a yellow oil: R_f 0.33 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=3421, 1716, 1589, 1575, 1479, 1423, 1356, 1283, 1247, 1231, 1092, 1038, 860, 773, 686 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.21 (s, 3H, CH_3CO), 3.16 (dd, J=13.8, 6.3 Hz, 1H, H-4), 3.43 (dd, J=13.8, 4.3 Hz, 1H, H-4), 3.69 (br s, 1H, OH), 3.80 (s, 3H, OCH_3), 4.29–4.37 (m, 1H, H-3), 6.77 (ddd, J=8.4, 2.7, 0.9 Hz, 1H, H-4′), 6.96 (t, J=3.3 Hz, 1H, H-2′), 6.99 (dm, J=8.4 Hz, 1H, H-6′), 7.21 (t, J=8.4 Hz, 1H, H-5′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.8 (CH_3CO), 38.1 (C-4), 55.2 (s, 3H, OCH_3), 75.4 (C-3), 112.6 (C-4′), 115.7 (C-2′), 122.4 (C-6′), 129.9 (C-5′), 136.1 (C-1′), 159.8 (C-3′), 208.0 (CH$_3$CO). MS (70 eV): m/z (%)=226 (M^+, 1), 165 (53), 153 (40), 140 (100), 139 (28), 125 (14), 107 (16), 77 (14). HRMS (EI) m/z [M^+] calcd for $C_{11}H_{14}O_3S$: 226.0664. Found: 226.0662.

*4.5.4. 4-((4-Chlorophenyl)thio)-3-hydroxybutan-2-one (**21d**).* According to the general procedure, by using **20d** (0.500 g, 1.31 mmol) and Li_2CO_3 (0.195 g, 2.63 mmol) in 20 mL of DMF/MeOH (1:1), **21d** (0.26 g, 85%) was obtained as a yellow oil: R_f 0.38 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=3424, 1717, 1573, 1476, 1414, 1389, 1357, 1274, 1164, 1093, 1010, 816, 743 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=2.20 (s, 3H, CH_3CO), 3.14 (dd, J=14.0, 6.0 Hz, 1H, H-4), 3.38 (dd, J=14.0, 4.0 Hz, 1H, H-4), 3.89 (br s, 1H, OH), 4.31 (dd, J=6.0, 4.0 Hz, 1H, H-3), 7.24–7.28 (m, 2H, H-3′), 7.33–7.36 (m, 2H, H-2′). ^{13}C NMR (125 MHz, $CDCl_3$): δ=25.6 (CH_3CO), 38.3 (C-4), 75.4 (C-3), 129.0 (C-3′), 131.6 (C-2′), 132.8 (C-4′), 133.6 (C-1′), 207.8 (CH$_3$CO). HRMS (EI) m/z [M^+] calcd for $C_{10}H_{11}O_2SCl$: 230.0168. Found: 230.0171.

*4.5.5. 4-((2-Bromophenyl)thio)-3-hydroxybutan-2-one (**21e**).* According to the general procedure, by using **20e** (0.600 g, 1.42 mmol) and Li_2CO_3 (0.209 g, 2.83 mmol) in 30 mL of DMF/MeOH (1:1), **21e** (0.34 g, 88%) was obtained as a yellow oil: R_f 0.38 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=3441, 1716, 1448, 1427, 1356, 1254, 1162, 1088, 1018, 746 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=2.26 (s, 3H, CH_3CO), 3.19 (dd, J=13.5, 6.0 Hz, 1H, H-4), 3.44 (dd, J=13.5, 4.0 Hz, 1H, H-4), 3.74 (br s, 1H, OH), 4.37 (dd, J=6.0, 4.0 Hz, 1H, H-3), 7.09 (td, J=8.0, 1.5 Hz, 1H, H-4′), 7.28 (td, J=8.0, 1.0 Hz, 1H, H-5′), 7.44 (dd, J=8.0, 1.5 Hz, 1H, H-6′), 7.57 (dd, J=8.0, 1.0 Hz, 1H, H-3′). ^{13}C NMR (125 MHz, $CDCl_3$): δ=25.8 (CH_3CO), 37.3 (C-4), 75.3 (C-3),

125.2 (C-2′), 127.9 (C-4′), 128.0 (C-5′), 130.6 (C-6′), 133.2 (C-3′), 136.0 (C-1′), 207.7 (CH_3CO). MS (70 eV): *m*/*z* (%)=275 (M^+, 1), 274 (6), 273 (4), 272 (4), 253 (51), 251 (30), 235 (25), 216 (61), 188 (41), 151 (59), 122 (97), 109 (100), 108 (68). HRMS (EI) *m*/*z* [M^+] calcd for $C_{10}H_{11}O_2SBr$: 273.9663. Found: 273.9651.

4.6. General procedures for the preparation of 10a–f, 11a, 17a–d, 18a,b, and 22a–g

Method A. A mixture of **7a**–**c**, **15a**,**b**, **15d**, **16a**,**b**, **21a**,**b** or **21d**,**e** and the isocyanates **9** was stirred and irradiated with MW (30–900 W) at 80–120 °C for 20–60 min. Afterward, CH_2Cl_2 (5 mL) was added, the mixture was stirred for 5 h and then filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 9:1) to give the desired product.

Method B. A mixture of **7a** or **15a** and the isocyanates **9b**,**c** was stirred and heated at 120 °C for 24 h under N_2 in an ACE pressure tube sealed with a Teflon screw cap. The mixture was diluted with CH_2Cl_2 (20 mL) and filtrated, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 95:5) to give the desired product.

*4.6.1. 5-(4-Methoxybenzyl)-4-methyl-3-phenyloxazol-2(3H)-one (**10a**).* According to Method A of the general procedure, by using **7a** (0.230 g, 1.19 mmol) and **9a** (0.19 g, 1.6 mmol) and irradiating (SEV, 900 W) at 80 °C for 20 min, **10a** (0.245 g, 70%) was obtained as a yellow solid: R_f 0.33 (hexane/EtOAc, 7:3); mp 99–101 °C. IR (film): $\overline{\nu}$=1749, 1701, 1599, 1503, 1452, 1381, 1299, 1243, 1175, 1033, 980, 818, 759, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.87 (br s, 3H, CH_3-4), 3.71 (br s, 2H, CH_2-5), 3.78 (s, 3H, CH_3O), 6.83–6.89 (m, 2H, H-3″), 7.16–7.20 (m, 2H, H-2″), 7.24–7.30 (m, 2H, H-2′), 7.32–7.40 (m, 1H, H-4′), 7.40–7.48 (m, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.7 (*C*H_3-4), 30.0 (*C*H_2-5), 55.1 (*C*H_3O), 114.0 (C-3″), 118.3 (C-4), 126.8 (C-2′), 128.2 (C-4′), 128.6 (C-1″), 129.3 (C-3′), 129.4 (C-2″), 133.6 (C-5), 134.9 (C-1′), 154.2 (C-2), 158.4 (C-4″). MS (70 eV): *m*/*z* (%)=296 (M^+, 1), 188 (33), 91 (8), 77 (100), 51 (51). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.10; H, 5.68; N, 4.75.

*4.6.2. 5-(3,4-Dimethoxybenzyl)-4-methyl-3-phenyloxazol-2(3H)-one (**10b**).* According to Method A of the general procedure, by using **7b** (0.200 g, 0.89 mmol) and **9a** (0.143 g, 1.20 mmol) and irradiating (SEV, 900 W) at 80 °C for 20 min, **10b** (0.197 g, 68%) was obtained as a yellow solid: R_f 0.38 (hexane/EtOAc, 7:3); mp 125–126 °C. IR (film): $\overline{\nu}$=1753, 1703, 1596, 1511, 1459, 1383, 1263, 1145, 1029, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.89 (br s, 3H, CH_3-4), 3.72 (br s, 2H, CH_2-5), 3.87 (s, 3H, CH_3O), 3.90 (s, 3H, CH_3O), 6.82 (br s, 3H, ArH″), 7.27–7.32 (m, 2H, H-2′), 7.35–7.42 (m, 1H, H-4′), 7.43–7.50 (m, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.9 (*C*H_3-4), 30.6 (*C*H_2-5), 55.8 (2*C*H_3O), 111.2 (C-2″), 111.7 (C-5″), 118.4 (C-4), 120.5 (C-6″), 126.9 (C-2′), 128.3 (C-4′), 129.2 (C-1″), 129.4 (C-3′), 133.7 (C-5), 134.8 (C-1′), 148.0 (C-4″), 149.0 (C-3″), 154.2 (C-2). MS (70 eV): *m*/*z* (%)=325 (M^+, 2), 280 (2), 118 (84), 77 (100), 51 (41). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.98; H, 5.87; N, 4.27.

*4.6.3. 4-Methyl-3-phenyl-5-(2,4,5-trimethoxybenzyl)oxazol-2(3H)-one (**10c**).* According to Method A of the general procedure, by using **7c** (0.200 g, 0.78 mmol) and **9a** (0.13 g, 1.1 mmol) and irradiating (SEV, 900 W) at 80 °C for 20 min, **10c** (0.217 g, 78%) was obtained as a yellow solid: R_f 0.13 (hexane/EtOAc, 7:3); mp 110–112 °C. IR (film): $\overline{\nu}$=1753, 1512, 1460, 1383, 1214, 1035 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.91 (br s, 3H, CH_3-4), 3.71 (br s, 2H, CH_2-5), 3.83 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 6.54 (s, 1H, H-3″), 6.85 (s, 1H, H-6″), 7.27–7.34 (m, 2H, H-2′), 7.36–7.41 (m, 1H, H-4′), 7.42–7.49 (m, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.7 (*C*H_3-4), 24.6 (*C*H_2-5), 56.1 (*C*H_3O), 56.2 (*C*H_3O), 56.7 (*C*H_3O), 97.3 (C-3″), 114.3 (C-6″), 116.2 (C-1″), 118.2 (C-4), 126.9 (C-2′), 128.1 (C-4′), 129.3 (C-3′), 133.8 (C-5), 134.7 (C-1′), 142.8 (C-5″), 148.6 (C-4″), 151.1 (C-2″), 154.6 (C-2). MS (70 eV): *m*/*z* (%)=355 (M^+, 100), 324 (41), 280 (97), 181 (21), 149 (30), 118 (99), 77 (69). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.57; H, 6.05; N, 4.06.

*4.6.4. 5-(4-Methoxybenzyl)-4-methyl-3-(p-tolyl)oxazol-2(3H)-one (**10d**).* According to Method B of the general procedure, by using **7a** (0.170 g, 0.876 mmol) and **9b** (0.28 g, 2.1 mmol), **10d** (0.173 g, 64%) was obtained as a yellow oil: R_f 0.50 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=1758, 1702, 1513, 1384, 1245, 1172, 1035, 983, 817, 752 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.85 (br s, 3H, CH_3-4), 2.37 (s, 3H, CH_3Ar), 3.70 (br s, 2H, CH_2-5), 3.78 (s, 3H, CH_3O), 6.84–6.88 (m, 2H, H-3″), 7.14–7.17 (m, 2H, H-2′), 7.17–7.21 (m, 2H, H-2″), 7.22–7.26 (m, 2H, H-3′). ^{13}C NMR (125 MHz, $CDCl_3$): δ=8.7 (*C*H_3-4), 21.0 (*C*H_3Ar), 30.1 (*C*H_2-5), 55.2 (*C*H_3O), 114.0 (C-3″), 118.5 (C-4), 126.8 (C-2′), 128.8 (C-1″), 129.5 (C-2″), 130.0 (C-3′), 131.1 (C-1′), 134.7 (C-5), 138.3 (C-4′), 154.6 (C-2), 158.5 (C-4″). MS (70 eV): *m*/*z* (%)=309 (M^+, 100), 278 (26), 264 (75), 132 (62), 91 (21). HRMS (EI) *m*/*z* [M^+] calcd for $C_{19}H_{19}NO_3$: 309.1365. Found: 309.1371.

*4.6.5. 3-(3-Chlorophenyl)-5-(4-methoxybenzyl)-4-methyloxazol-2(3H)-one (**10e**).* According to Method B of the general procedure, by using **7a** (0.140 g, 0.722 mmol) and **9c** (0.166 g, 1.08 mmol), **10e** (0.123 g, 52%) was obtained as a yellow oil: R_f 0.55 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=1757, 1703, 1593, 1512, 1483, 1378, 1245, 1176, 1035, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.91 (br s, 3H, CH_3-4), 3.71 (br s, 2H, CH_2-5), 3.80 (s, 3H, CH_3O), 6.83–6.92 (m, 2H, H-3″), 7.16–7.25 (m, 3H, H-6′, H-2″), 7.31–7.34 (m, 1H, H-2′), 7.35–7.44 (m, 2H, H-4′, H-5′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=9.0 (*C*H_3-4), 30.1 (*C*H_2-5), 55.3 (*C*H_3O), 114.1 (C-3″), 118.0 (C-4), 125.1 (C-6′), 127.1 (C-2′), 128.4 (C-1″), 128.5 (C-4′), 129.5 (C-2″), 130.4 (C-5′), 134.8 (C-1′), 135.0 (C-3′), 135.5 (C-5), 158.6 (C-4″). MS (70 eV): *m*/*z* (%)=331 (M^++2, 30), 329 (M^+, 93), 298 (46), 286 (40), 284 (100), 270 (21), 254 (20), 154 (22), 152 (62), 121 (16), 111 (20). HRMS (EI) *m*/*z* [M^+] calcd for $C_{18}H_{16}ClNO_3$: 329.0819. Found: 329.0810.

*4.6.6. 3-(4-Chlorophenyl)-5-(4-methoxybenzyl)-4-methyloxazol-2(3H)-one (**10f**).* According to Method A of the general procedure, by using **7a** (0.216 g, 1.11 mmol) and **9d** (0.341 g, 2.22 mmol) and irradiating (CEM, 30 W) at 120 °C for 60 min, **10f** (0.23 g, 63%) was obtained as a white solid: R_f 0.40 (hexane/EtOAc, 7:3); mp 132–134 °C. IR (film): $\overline{\nu}$=1749, 1701, 1509, 1494, 1380, 1242, 1168, 1088, 1031, 981, 829, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.87 (br s, 3H, CH_3-4), 3.70 (br s, 2H, CH_2-5), 3.78 (s, 3H, CH_3O), 6.82–6.89 (m, 2H, H-3″), 7.15–7.21 (m, 2H, H-2″), 7.21–7.27 (m, 1H, H-2′), 7.39–7.42 (m, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.7 (*C*H_3-4), 30.0 (*C*H_2-5), 55.2 (*C*H_3O), 114.0 (C-3″), 118.0 (C-4), 128.1 (C-2′), 128.5 (C-1″), 129.4 (C-2″), 129.5 (C-3′), 132.2 (C-1′), 134.0 (C-4′), 135.2 (C-5), 154.2 (C-2), 158.5 (C-4″). Anal. Calcd for $C_{18}H_{16}NO_3Cl$: C, 65.56; H, 4.89; N, 4.25. Found: C, 65.52; H, 4.92; N, 4.21.

*4.6.7. 5-(3,4-Dimethoxybenzyl)-4-methylene-3-phenyloxazolidin-2-one (**11a**).* According to Method A of the general procedure, by using **7b** (0.200 g, 0.89 mmol) and **9a** (0.143 g, 1.20 mmol) and irradiating (200 W) at 80 °C for 20 min, **11a** (0.218 g, 75%) was obtained as a white solid: R_f 0.19 (hexane/EtOAc, 7:3); mp 158–160 °C. IR (film): $\overline{\nu}$=1752, 1702, 1595, 1508, 1457, 1383, 1261, 1236, 1185, 1145, 1027, 761, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.99 (dd, *J*=14.4, 5.1 Hz, 1H, CH_2-5), 3.24 (dd, *J*=14.4, 4.2 Hz, 1H, CH_2-5), 3.83 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 4.10 (dd, *J*=2.7, 1.8 Hz, 1H, CH_2=),

4.17 (dd, *J*=2.7, 2.4 Hz, 1H, C*H*$_2$=), 5.35–5.41 (m, 1H, H-5), 6.80–6.87 (m, 3H, ArH″), 6.96–7.02 (m, 2H, H-2′), 7.29–7.43 (m, 3H, H-3′, H-4′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=40.7 (*C*H$_2$-5), 55.85 (*C*H$_3$O), 55.87 (*C*H$_3$O), 78.4 (C-5), 82.8 (*C*H$_2$=), 110.9 (C-2″), 113.1 (C-5″), 122.3 (C-6″), 126.4 (C-1″), 126.9 (C-2′), 128.3 (C-4′), 129.5 (C-3′), 133.4 (C-1′), 145.1 (C-4), 148.2 (C-4″), 148.6 (C-3″), 155.1 (C-2). MS (70 eV): *m*/*z* (%)=326 (M^++1, 1), 118 (76), 77 (100), 51 (37). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.92; H, 5.90; N, 3.99.

*4.6.8. 5-(Furan-2-ylmethyl)-4-methyl-3-(phenyl)oxazol-2(3H)-one (**17a**).* According to Method A of the general procedure, by using **15a** (0.262 g, 1.70 mmol) and **9a** (0.297 g, 2.50 mmol) and irradiating (SEV, 900 W) at 80 °C for 20 min, **17a** (0.32 g, 74%) was obtained as a pale yellow solid: R_f 0.38 (hexane/EtOAc, 7:3); mp 94–96 °C. IR (film): $\overline{\nu}$=1762, 1706, 1596, 1498, 1382, 1236, 1175, 1040, 1006, 980, 742, 694 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.85 (t, *J*=0.8 Hz, 3H, C*H*$_3$-4), 3.81 (br s, 2H, C*H*$_2$-5), 6.19 (ddt, *J*=3.3, 1.7, 0.8 Hz, 1H, H-3″), 6.32 (dd, *J*=3.3, 0.9 Hz, 1H, H-4″), 7.26–7.32 (m, 2H, H-2′), 7.33–7.35 (m, 1H, H-5″), 7.35–7.41 (m, 1H, H-4′), 7.42–7.49 (m, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.5 (*C*H$_3$-4), 24.0 (*C*H$_2$-5), 107.0 (C-3″), 110.5 (C-4″), 119.3 (C-4), 126.8 (C-2′), 128.3 (C-4′), 129.3 (C-3′), 131.7 (C-5), 133.5 (C-1′), 141.6 (C-5″), 149.6 (C-2″), 154.3 (C-2). MS (70 eV): *m*/*z* (%)=255 (M^+, 58), 210 (17), 182 (94), 167 (28), 118 (100), 77 (90). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.64; H, 5.18; N, 5.51.

*4.6.9. 5-(Furan-2-ylmethyl)-4-methyl-3-(p-tolyl)oxazol-2(3H)-one (**17b**).* According to Method B of the general procedure, by using **15a** (0.100 g, 0.649 mmol) and **9b** (0.207 g, 1.56 mmol), **17b** (0.121 g, 70%) was obtained as a pale brown solid: R_f 0.40 (hexane/EtOAc, 7:3); mp 95–97 °C. IR (KBr): $\overline{\nu}$=1753, 1704, 1515, 1390, 1238, 1179, 1038, 983, 824, 755 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.82 (br s, 3H, C*H*$_3$-4), 2.38 (s, 3H, C*H*$_3$Ar), 3.81 (br s, 2H, C*H*$_2$-5), 6.18 (dd, *J*=3.0, 1.0 Hz, 1H, H-3″), 6.32 (br d, *J*=3.0 Hz, 1H, H-4″), 7.15–7.19 (m, 2H, H-2′), 7.24–7.28 (m, 2H, H-3′), 7.34 (br d, *J*=1.0 Hz, 1H, H-5″). ^{13}C NMR (125 MHz, $CDCl_3$): δ=8.5 (*C*H$_3$-4), 21.1 (*C*H$_3$Ar), 24.1 (*C*H$_2$-5), 107.0 (C-3″), 110.6 (C-4″), 119.5 (C-4), 126.8 (C-2′), 130.0 (C-3′), 131.0 (C-1′), 131.7 (C-5), 138.5 (C-4′), 141.7 (C-5″), 149.8 (C-2″), 154.5 (C-2). MS (70 eV): *m*/*z* (%)=269 (M^+, 100), 196 (58), 184 (18), 132 (74), 91 (35). HRMS (EI) *m*/*z* [M^+] calcd for $C_{16}H_{15}NO_3$: 269.1052. Found: 269.1058.

*4.6.10. 4-Methyl-3-phenyl-5-(thiophen-2-ylmethyl)oxazol-2(3H)-one (**17c**).* According to Method A of the general procedure, by using **15b** (0.112 g, 0.66 mmol) and **9a** (0.094 g, 0.79 mmol) and irradiating (SEV, 900 W) at 80 °C for 20 min, **17c** (0.143 g, 80%) was obtained as a pale brown solid: R_f 0.41 (hexane/EtOAc, 7:3); mp 98–100 °C. IR (film): $\overline{\nu}$=1752, 1705, 1596, 1499, 1380, 1178, 1038, 979, 758, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.90 (t, *J*=0.6 Hz, 3H, C*H*$_3$-4), 3.98 (br s, 2H, C*H*$_2$-5), 6.94–6.98 (m, 2H, H-3″, H-4″), 7.18–7.21 (m, 1H, H-5″), 7.28–7.33 (m, 2H, H-2′), 7.36–7.43 (m, 1H, H-4′), 7.43–7.51 (m, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.8 (*C*H$_3$-4), 25.3 (*C*H$_2$-5), 118.9 (C-4), 124.4 (C-5″), 125.8 (C-3″), 126.9 (C-2′), 127.1 (C-4″), 128.4 (C-4′), 129.4 (C-3′), 133.6 (C-5), 133.8 (C-1′), 138.8 (C-2″), 154.4 (C-2). MS (70 eV): *m*/*z* (%)=271 (M^+, 76), 226 (66), 212 (55), 182 (21), 118 (100), 77 (92). Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.55; H, 4.76; N, 5.20.

*4.6.11. 4-Methyl-5-((1H-pyrrol-2-yl)methyl)-3-(p-tolyl)oxazol-2(3H)-one (**17d**).* According to Method A of the general procedure, by using **15d** (0.100 g, 0.649 mmol) and **9b** (0.207 g, 1.56 mmol) and irradiating (CEM, 30 W) at 120 °C for 60 min, **17d** (0.170 g, 65%) was obtained as a pale brown oil: R_f 0.42 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=3326, 2924, 1744, 1699, 1600, 1517, 1387, 1315, 1187, 1171, 1041, 988, 818, 751 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.82 (s, 3H, C*H*$_3$-4), 2.38 (s, 3H, C*H*$_3$Ar), 3.79 (s, 2H, C*H*$_2$-5), 6.02 (br s, 1H, H-3″), 6.14 (dd, *J*=4.5, 2.7 Hz, 1H, H-4″), 6.73–6.76 (m, 1H, H-5″), 7.12–7.17 (m, 2H, H-2′), 7.23–7.28 (m, 2H, H-3′), 8.39 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=8.6 (*C*H$_3$-4), 21.1 (*C*H$_3$Ar), 23.4 (*C*H$_2$-5), 106.4 (C-3″), 108.3 (C-4″), 117.8 (C-5″), 118.7 (C-4), 126.1 (C-2″), 126.9 (C-2′), 130.1 (C-3′), 130.9 (C-1′), 133.4 (C-5), 138.6 (C-4′), 154.6 (C-2). HRMS (EI) *m*/*z* [M^+] calcd for $C_{16}H_{16}N_2O_2$: 268.1212. Found: 268.1217.

*4.6.12. 5,5′-(Furan-2,5-diylbis(methylene))bis(4-methyl-3-phenyloxazol-2(3H)-one) (**18a**).* According to Method A of the general procedure, by using **16a** (0.175 g, 0.73 mmol) and **9a** (0.19 g, 1.6 mmol) and irradiating (SEV, 900 W) at 80 °C for 20 min, **18a** (0.174 g, 54%) was obtained as a pale yellow solid: R_f 0.30 (hexane/EtOAc, 1:1). IR (film): $\overline{\nu}$=1754, 1704, 1597, 1499, 1382, 1178, 979, 758, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.87 (s, 6H, 2C*H*$_3$-4), 3.80 (s, 4H, 2C*H*$_2$-5), 6.12 (s, 2H, H-3″, H-4″), 7.26–7.33 (m, 4H, Ph–H), 7.35–7.50 (m, 6H, Ph–H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.7 (2C*H*$_3$-4), 24.1 (2C*H*$_2$-5), 108.0 (C-3″, C-4″), 119.4 (2C-4), 126.9 (4C-2′), 128.4 (2C-4′), 129.4 (4C-3′), 131.8 (2C-5), 133.6 (2C-1′), 149.0 (C-2″, C-5″), 154.3 (2C-2). HRMS (EI) *m*/*z* [M^+] calcd for $C_{26}H_{22}N_2O_5$: 442.1529. Found: 442.1522.

*4.6.13. 5,5′-(Thiophene-2,5-diylbis(methylene))bis(4-methyl-3-(p-tolyl)oxazol-2(3H)-one) (**18b**).* According to Method A of the general procedure, by using **16b** (0.045 g, 0.18 mmol) and **9b** (0.070 g, 0.53 mmol) and irradiating (CEM, 30 W) at 120 °C for 30 min, **18b** (0.043 g, 51%) was obtained as a pale yellow oil: R_f 0.30 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=2920, 1757, 1700, 1515, 1384, 818, 751 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.89 (s, 6H, 2C*H*$_3$-4), 2.38 (s, 6H, 2Ar–C*H*$_3$), 3.91 (s, 4H, 2C*H*$_2$-5), 6.77 (s, 2H, H-3″, H-4″), 7.17–7.20 (m, 4H, 2Ar–H), 7.24–7.27 (m, 2H, 2Ar–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=8.8 (2CH$_3$-4), 21.1 (2Ar–*C*H$_3$), 25.6 (2CH$_2$-5), 119.1 (2C-4), 125.7 (C-3″, C-4″), 126.9 (4C-2′), 130.1 (4C-3′), 130.9 (2C-1′), 133.5 (2C-5), 138.2 (C-2″, C-5″), 138.6 (2C-4′), 154.6 (2C-2). HRMS (EI) *m*/*z* [M^+] calcd for $C_{28}H_{26}N_2O_4S$: 486.1613. Found: 486.1633.

*4.6.14. 3-(3-Chlorophenyl)-4-methyl-5-((phenylthio)methyl)oxazol-2(3H)-one (**22a**).* According to Method A of the general procedure, by using **21a** (0.079 g, 0.403 mmol) and **9c** (0.070 g, 0.53 mmol) and irradiating (CEM, 100 W) at 100 °C for 40 min, **22a** (0.084 g, 63%) was obtained as a pale yellow oil: R_f 0.48 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=1757, 1698, 1593, 1482, 1437, 1377, 1276, 1185, 1041, 1002, 788, 765, 749, 692 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.51 (s, 3H, C*H*$_3$-4), 3.84 (br s, 2H, C*H*$_2$-5), 7.08–7.13 (m, 1H, H-6′), 7.21–7.24 (m, 1H, H-2′), 7.30–7.40 (m, 5H, Ar–H), 7.43–7.48 (m, 2H, H-2″). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.4 (*C*H$_3$-4), 30.1 (*C*H$_2$-5), 120.7 (C-4), 125.0 (C-6′), 127.1 (C-2′), 128.1 (C-4″), 128.7 (C-4′), 129.0 (C-3″), 130.4 (C-5′), 131.8 (C-5), 133.3 (C-2″), 134.0 (C-1″), 134.5 (C-1′), 135.0 (C-3′), 153.7 (C-2). MS (70 eV): *m*/*z* (%)=332 (M^+, 1), 224 (32), 222 (100), 178 (22), 143 (36), 115 (12). HRMS (EI) *m*/*z* [M^+] calcd for $C_{17}H_{14}ClNO_2S$: 331.0434. Found: 331.0441.

*4.6.15. 4-Methyl-3-phenyl-5-((m-tolylthio)methyl)oxazol-2(3H)-one (**22b**).* According to Method A of the general procedure, by using **21b** (0.130 g, 0.619 mmol) and **9a** (0.176 g, 1.48 mmol) and irradiating (CEM, 300 W) at 120 °C for 40 min, **22b** (0.11 g, 57%) was obtained as a pale yellow oil: R_f 0.50 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=1756, 1697, 1596, 1501, 1381, 1270, 1185, 1040, 981, 764, 692 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.52 (s, 3H, C*H*$_3$-4), 2.33 (s, 3H, C*H*$_3$Ar), 3.84 (s, 2H, C*H*$_2$-5), 7.11 (br d, *J*=7.5 Hz, 1H, H-4″), 7.18–7.20 (m, 2H, H-2′), 7.21–7.33 (m, 3H, H-2″, H-5″, H-6″), 7.36–7.40 (m, 1H, H-4′), 7.42–7.46 (m, 2H, H-3′). ^{13}C NMR (125 MHz, $CDCl_3$): δ=8.4 (*C*H$_3$-4), 21.2 (*C*H$_3$Ar), 30.1 (*C*H$_2$-5), 121.1 (C-4), 126.9 (C-2′), 128.5 (C-4′), 128.7 (C-4″), 128.8 (C-5″), 129.5 (C-3′), 130.1 (C-6″), 131.5 (C-

5), 133.4 (C-1′), 133.9 (C-2″), 133.9 (C-1″), 138.8 (C-3″), 154.1 (C-2). MS (70 eV): *m*/*z* (%)=311 (M^+, 1), 246 (12), 187 (15), 143 (38), 124 (51), 91 (100), 77 (38). HRMS (EI) *m*/*z* [M^+] calcd for $C_{18}H_{17}NO_2S$: 311.0980. Found: 311.0971.

*4.6.16. 4-Methyl-3-(p-tolyl)-5-((m-tolylthio)methyl)oxazol-2(3H)-one (**22c**).* According to Method A of the general procedure, by using **21b** (0.117 g, 0.56 mmol) and **9b** (0.178 g, 1.34 mmol) and irradiating (CEM, 300 W) at 120 °C for 40 min, **22c** (0.134 g, 74%) was obtained as a pale yellow oil: R_f 0.50 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$=1760, 1697, 1517, 1383, 1270, 1188, 1173, 1039, 984, 818, 780, 754, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.47 (s, 3H, C*H*$_3$-4), 2.31 (s, 3H, *m*-C*H*$_3$Ar), 2.36 (s, 3H, *p*-C*H*$_3$Ar), 3.82 (s, 2H, C*H*$_2$-5), 7.03–7.12 (m, 3H, H-2′, H-4″), 7.15–7.27 (m, 5H, H-3′, H-2″, H-5″, H-6″). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.2 (*C*H$_3$-4), 20.9 (*p*-*C*H$_3$Ar), 21.1 (*m*-*C*H$_3$Ar), 29.9 (*C*H$_2$-5), 121.2 (C-4), 126.5 (C-2′), 128.5 (C-4″), 128.7 (C-5″), 129.91 (C-3′), 129.93 (C-6″), 130.6 (C-1′), 131.0 (C-5), 133.6 (C-2″), 133.7 (C-1″), 138.4 (C-3″), 138.6 (C-4′), 154.1 (C-2). MS (70 eV): *m*/*z* (%)=325 (M^+, 1), 246 (62), 213 (34), 202 (100), 186 (42), 158 (48), 124 (47), 107 (45), 91 (90), 77 (32). HRMS (EI) *m*/*z* [M^+] calcd for $C_{19}H_{19}NO_2S$: 325.1136. Found: 325.1149.

*4.6.17. 3-(4-Methoxyphenyl)-4-methyl-5-((m-tolylthio)methyl)oxazol-2(3H)-one (**22d**).* According to Method A of the general procedure, by using **21b** (0.100 g, 0.476 mmol) and **9e** (0.170 g, 1.14 mmol) and irradiating (CEM, 300 W) at 120 °C for 40 min, **22d** (0.120 g, 74%) was obtained as a pale yellow oil: R_f 0.38 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$=1759, 1515, 1385, 1250, 1168, 1036, 982, 833, 781, 755, 680 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.48 (s, 3H, C*H*$_3$-4), 2.32 (s, 3H, C*H*$_3$Ar), 3.81 (s, 3H, C*H*$_3$O), 3.83 (s, 2H, C*H*$_2$-5), 6.92–6.96 (m, 2H, H-3′), 7.08–7.12 (m, 3H, H-2′, H-4″), 7.20 (t, *J*=8.0 Hz, 1H, H-5″), 7.22–7.27 (m, 2H, H-2″, H-6″). ^{13}C NMR (125 MHz, $CDCl_3$): δ=8.2 (*C*H$_3$-4), 21.1 (*C*H$_3$Ar), 30.0 (*C*H$_2$-5), 55.4 (*C*H$_3$O), 114.7 (C-3′), 121.4 (C-4), 126.0 (C-1′), 128.2 (C-2′), 128.6 (C-4″), 128.8 (C-5″), 130.0 (C-6″), 131.0 (C-5), 133.6 (C-2″), 134.0 (C-1″), 138.7 (C-3″), 154.4 (C-2), 159.5 (C-4′). MS (70 eV): *m*/*z* (%)=341 (M^+, 1), 250 (46), 244 (70), 213 (61), 212 (90), 197 (100), 180 (74), 164 (62), 121 (77), 102 (64), 90 (99), 88 (94). HRMS (EI) *m*/*z* [M^+] calcd for $C_{19}H_{19}NO_3S$: 341.1086. Found: 341.1089.

*4.6.18. 5-(((4-Chlorophenyl)thio)methyl)-4-methyl-3-(p-tolyl)oxazol-2(3H)-one (**22e**).* According to Method A of the general procedure, by using **21d** (0.107 g, 0.46 mmol) and **9b** (0.148 g, 1.11 mmol) and irradiating (CEM, 300 W) at 120 °C for 40 min, **22e** (0.110 g, 69%) was obtained as a pale yellow solid: R_f 0.46 (hexane/EtOAc, 7:3); mp 91–93 °C. IR (film): $\bar{\nu}$=1760, 1696, 1517, 1475, 1385, 1271, 1189, 1094, 1040, 1012, 984, 818, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.55 (s, 3H, C*H*$_3$-4), 2.36 (s, 3H, C*H*$_3$Ar), 3.83 (s, 2H, C*H*$_2$-5), 7.04–7.10 (m, 2H, H-2′), 7.22–7.26 (m, 2H, H-3′), 7.26–7.31 (m, 2H, H-2″), 7.34–7.40 (m, 2H, H-3″). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.4 (*C*H$_3$-4), 21.0 (*C*H$_3$Ar), 30.1 (*C*H$_2$-5), 121.4 (C-4), 126.6 (C-2′), 129.0 (C-2″), 130.1 (C-3′), 130.5 (C-1′), 130.9 (C-5), 132.7 (C-4″), 134.0 (C-1″), 134.2 (C-3″), 138.7 (C-4′), 154.1 (C-2). MS (70 eV): *m*/*z* (%)=346 (M^++1, 1), 253 (63), 251 (40), 235 (33), 203 (15), 144 (94), 133 (97), 131 (78), 109 (84), 104 (100), 91 (78), 77 (68). HRMS (EI) *m*/*z* [M^+] calcd for $C_{18}H_{16}ClNO_2S$: 345.0590. Found: 345.0596.

*4.6.19. 5-(((4-Chlorophenyl)thio)methyl)-3-(4-methoxyphenyl)-4-methyloxazol-2(3H)-one (**22f**).* According to Method A of the general procedure, by using **21d** (0.090 g, 0.39 mmol) and **9e** (0.139 g, 0.93 mmol) and irradiating (CEM, 300 W) at 120 °C for 40 min, **22f** (0.086 g, 61%) was obtained as a pale yellow oil: R_f 0.36 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$=1758, 1515, 1475, 1387, 1250, 1169, 1094, 1036, 1012, 983, 832 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.47 (s, 3H, C*H*$_3$-4), 3.75 (s, 3H, C*H*$_3$O), 3.76 (s, 2H, C*H*$_2$-5), 6.84–6.94 (m, 2H, H-3′), 7.02–7.08 (m, 2H, H-2′), 7.19–7.26 (m, 2H, H-2″), 7.28–7.35 (m, 2H, H-3″). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.4 (*C*H$_3$-4), 30.1 (*C*H$_2$-5), 55.5 (*C*H$_3$O), 114.7 (C-3′), 121.6 (C-4), 125.8 (C-1′), 128.3 (C-2′), 129.1 (C-2″), 130.8 (C-5), 132.8 (C-4″), 134.1 (C-1″), 134.3 (C-3″), 154.3 (C-2), 159.5 (C-4′). MS (70 eV): *m*/*z* (%)=362 (M^++1, 1), 286 (39), 253 (37), 184 (23), 149 (84), 143 (100), 109 (63), 108 (92), 77 (32). HRMS (EI) *m*/*z* [M^+] calcd for $C_{18}H_{16}ClNO_3S$: 361.0539. Found: 361.0524.

*4.6.20. 5-(((2-Bromophenyl)thio)methyl)-4-methyl-3-(p-tolyl)oxazol-2(3H)-one (**22g**).* According to Method A of the general procedure, by using **21e** (0.070 g, 0.255 mmol) and **9b** (0.081 g, 0.611 mmol) and irradiating (CEM, 300 W) at 120 °C for 40 min, **22g** (0.062 g, 63%) was obtained as a pale yellow oil: R_f 0.44 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$=1760, 1696, 1516, 1448, 1384, 1271, 1188, 1039, 1019, 984, 818, 752 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.52 (s, 3H, C*H*$_3$-4), 2.37 (s, 3H, C*H*$_3$Ar), 3.91 (s, 2H, C*H*$_2$-5), 7.04–7.08 (m, 2H, H-2′), 7.16 (td, *J*=8.0, 1.5 Hz, 1H, H-4″), 7.21–7.26 (m, 2H, H-3′), 7.28 (td, *J*=8.0, 1.0 Hz, 1H, H-5″), 7.52 (dd, *J*=8.0, 1.5 Hz, 1H, H-6″), 7.61 (dd, *J*=8.0, 1.0 Hz, 1H, H-3″). ^{13}C NMR (125 MHz, $CDCl_3$): δ=8.3 (*C*H$_3$-4), 21.1 (*C*H$_3$Ar), 28.9 (*C*H$_2$-5), 121.7 (C-4), 126.8 (C-2′), 128.0 (C-5″), 128.2 (C-2″), 129.3 (C-4″), 130.1 (C-3′), 130.6 (C-1′), 130.7 (C-5), 133.2 (C-3″), 134.6 (C-6″), 135.2 (C-1″), 138.7 (C-4′), 154.2 (C-2). MS (70 eV): *m*/*z* (%)=390 (M^+, 1), 310 (6), 252 (80), 250 (66), 215 (73), 187 (47), 183 (100), 156 (47), 128 (70), 105 (72), 102 (81). HRMS (EI) *m*/*z* [M^+] calcd for $C_{18}H_{16}BrNO_2S$: 389.0085. Found: 389.0077.

4.7. General procedure for the preparation of 26a–d

To a solution of **1a** (1.1 mol equiv) in dry CH_2Cl_2 (10 mL) at 0 °C a 1.0 M solution of $ZnCl_2$ in Et_2O (2.7 mol equiv) and **23** (1.0 mol equiv) were added, and the mixture was stirred at room temperature under nitrogen for 48 h. A saturated aqueous solution of $NaHCO_3$ (15 mL) was added and the mixture was extracted with CH_2Cl_2 (2×15 mL). The organic layer was washed with water (2×15 mL) and dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 9:1) to give the desired products **26a–d**.

*4.7.1. 1-(1H-Indol-3-yl)-3-oxobutan-2-yl 4-nitrobenzoate (**26a**).* According to the general procedure, by using **1a** (1.105 g, 4.70 mmol), **23a** (0.500 g, 4.27 mmol), and $ZnCl_2$ (1.742 g, 12.81 mmol), **26a** (1.47 g, 98%) was obtained as an orange solid: R_f 0.30 (hexane/EtOAc, 7:3); mp 144–146 °C. IR (film): $\bar{\nu}$=3410, 1717, 1524, 1345, 1279, 1102, 1013, 871, 846, 745, 718 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=2.07 (s, 3H, C*H*$_3$CO), 3.30–3.40 (m, 2H, H-1′), 5.50 (t, *J*=6.3 Hz, 1H, H-2′), 7.00 (s, 1H, H-2″), 7.06 (t, *J*=7.5 Hz, 1H, H-5″), 7.14 (t, *J*=7.5 Hz, 1H, H-6″), 7.29 (d, *J*=7.5 Hz, 1H, H-7″), 7.56 (d, *J*=7.5 Hz, 1H, H-4″), 8.03–8.07 (m, 2H, H-2), 8.10 (br s, 1H, NH), 8.12–8.18 (m, 2H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ=26.6 (C-1′), 27.1 (*C*H$_3$CO), 80.0 (C-2′), 109.6 (C-3″), 111.4 (C-7″), 118.6 (C-4″), 119.8 (C-5″), 122.5 (C-6″), 122.9 (C-2″), 123.5 (C-3), 127.3 (C-3a″), 131.0 (C-2), 134.7 (C-1), 136.1 (C-7a″), 150.7 (C-4), 164.3 (Ar*C*O$_2$), 204.7 (CH$_3$*C*O). MS (70 eV): *m*/*z* (%)=352 (M^+, 3), 253 (15), 251 (13), 186 (14), 185 (100), 184 (46), 170 (50), 150 (6), 130 (72). Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.78; H, 4.60; N, 7.96.

*4.7.2. 1-(1-Allyl-1H-indol-3-yl)-3-oxobutan-2-yl 4-nitrobenzoate (**26b**).* According to the general procedure, by using **1a** (0.165 g, 0.70 mmol), **23b** (0.100 g, 0.64 mmol), and $ZnCl_2$ (0.261 g, 1.92 mmol), **26b** (0.174 g, 70%) was obtained as a pale yellow oil: R_f 0.64 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$=1721, 1607, 1526, 1467, 1349, 1277, 1116, 1102, 1014, 872, 844, 743, 719 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=2.14 (s, 3H, C*H*$_3$CO), 3.37–3.47 (m, 2H, H-1′), 4.67 (dt, *J*=5.5, 2.0 Hz, 2H, H-1‴), 5.02 (dm, *J*=17.0 Hz, 1H, H-3‴), 5.16 (dm, *J*=10.0 Hz, 1H, H-3‴), 5.55 (dd, *J*=7.0, 5.5 Hz, 1H, H-2′), 5.94 (ddt, *J*=17.0, 10.0, 5.5 Hz, 1H, H-2‴), 6.98 (s, 1H, H-2″), 7.13 (ddd, *J*=8.0, 7.0,

1.0 Hz, 1H, H-5″), 7.23 (ddd, *J*=8.5, 7.0, 1.5 Hz, 1H, H-6″), 7.30 (d, *J*=8.5 Hz, 1H, H-7″), 7.63 (d, *J*=8.0 Hz, 1H, H-4″), 8.12–8.16 (m, 2H, H-2), 8.23–8.26 (m, 2H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ=26.6 (C-1′), 27.2 (*C*H$_3$CO), 48.6 (C-1‴), 80.0 (C-2′), 108.5 (C-3″), 109.8 (C-7″), 117.2 (C-3‴), 118.8 (C-4″), 119.4 (C-5″), 122.1 (C-6″), 123.5 (C-3), 126.6 (C-2″), 127.9 (C-3a″), 131.0 (C-2), 133.3 (C-2‴), 134.8 (C-1), 136.4 (C-7a″), 150.7 (C-4), 164.2 (Ar*C*O$_2$), 204.7 (CH$_3$*C*O). Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 67.32; H, 5.17; N, 7.14.

*4.7.3. 3-Oxo-1-(1-(prop-2-yn-1-yl)-1H-indol-3-yl)butan-2-yl 4-nitrobenzoate (**26c**).* According to the general procedure, by using **1a** (0.500 g, 2.13 mmol), **23c** (0.300 g, 1.94 mmol), and $ZnCl_2$ (0.792 g, 5.82 mmol), **26c** (0.620 g, 82%) was obtained as a yellow solid: R_f 0.40 (hexane/EtOAc, 7:3); mp 88–89 °C. IR (film): $\overline{\nu}$=3285, 2124, 1721, 1607, 1527, 1467, 1349, 1276, 1182, 1117, 1103, 1014, 872, 844, 743, 719 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.15 (s, 3H, C*H*$_3$CO), 2.38 (t, *J*=3.3 Hz, 1H, H-3‴), 3.36–3.46 (m, 2H, H-1′), 4.83 (d, *J*=3.3 Hz, 2H, H-1‴), 5.55 (dd, *J*=7.0, 5.5 Hz, 1H, H-2′), 7.11 (s, 1H, H-2″), 7.16 (td, *J*=8.0, 1.0 Hz, 1H, H-5″), 7.27 (td, *J*=8.0, 1.0 Hz, 1H, H-6″), 7.38 (d, *J*=8.0 Hz, 1H, H-7″), 7.64 (d, *J*=8.0 Hz, 1H, H-4″), 8.12–8.16 (m, 2H, H-2), 8.22–8.26 (m, 2H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ=26.5 (C-1′), 27.1 (*C*H$_3$CO), 35.7 (C-1‴), 73.6 (C-3‴), 77.5 (C-2‴), 79.9 (C-2′), 109.3 (C-3″), 109.6 (C-7″), 119.0 (C-4″), 119.9 (C-5″), 122.4 (C-6″), 123.5 (C-3), 126.0 (C-2″), 128.2 (C-3a″), 131.1 (C-2), 134.7 (C-1), 136.0 (C-7a″), 150.7 (C-4), 164.2 (Ar*C*O$_2$), 204.6 (CH$_3$*C*O). Anal. Calcd for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.70; H, 4.63; N, 7.16.

*4.7.4. 1-(1-(3-Methoxybenzyl)-1H-indol-3-yl)-3-oxobutan-2-yl 4-nitrobenzoate (**26d**).* According to the general procedure, by using **1a** (0.632 g, 2.69 mmol), **23d** (0.578 g, 2.45 mmol), and $ZnCl_2$ (1.000 g, 7.35 mmol), **26d** (0.851 g, 74%) was obtained as a yellow solid: R_f 0.46 (hexane/EtOAc, 7:3); mp 150–151 °C. IR (film): $\overline{\nu}$=1719, 1602, 1525, 1490, 1466, 1437, 1347, 1266, 1167, 1102, 1041, 1013, 871, 843, 781, 743, 718 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.13 (s, 3H, C*H*$_3$CO), 3.33–3.49 (m, 2H, H-1′), 3.67 (s, 3H, C*H*$_3$O), 5.20 (s, 2H, C*H*$_2$–N), 5.55 (dd, *J*=7.2, 5.7 Hz, 1H, H-2′), 6.56–6.60 (m, 1H, H-2‴), 6.63 (br d, *J*=7.5 Hz, 1H, H-6‴), 6.75 (dd, *J*=8.1, 2.4 Hz, 1H, H-4‴), 7.00 (s, 1H, H-2″), 7.09–7.23 (m, 3H, H-5″, H-6″, H-5‴), 7.28 (br d, *J*=7.8 Hz, 1H, H-7″), 7.63 (dd, *J*=7.6, 0.6 Hz, 1H, H-4″), 8.04–8.09 (m, 2H, H-2), 8.13–8.19 (m, 2H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.5 (C-1′), 27.0 (*C*H$_3$CO), 49.7 (*C*H$_2$–N), 55.0 (*C*H$_3$O), 79.7 (C-2′), 108.7 (C-3″), 109.8 (C-7″), 112.4 (C-4‴), 112.8 (C-2‴), 118.7 (C-4″), 118.9 (C-6‴), 119.4 (C-5″), 122.1 (C-6″), 123.4 (C-3), 126.9 (C-2″), 127.8 (C-3a″), 129.7 (C-5‴), 130.8 (C-2), 134.6 (C-1), 136.5 (C-7a″), 138.8 (C-1‴), 150.5 (C-4), 159.8 (C-3‴), 164.1 (Ar*C*O$_2$), 204.6 (CH$_3$*C*O). HRMS (EI) *m*/*z* [M$^+$] calcd for $C_{27}H_{24}N_2O_6$: 472.1634. Found: 472.1643.

4.8. General procedure for the preparation of 24a–d

A mixture of **26** (1.0 mol equiv) and K_2CO_3 (2.0–3.0 mol equiv) in THF/MeOH (1:1) (20 mL) was stirred at room temperature for 30 min. Afterward a saturated aqueous solution of NH_4Cl (10 mL) was added, then extracted with EtOAc (2×10 mL). The organic layer was washed with water (2×10 mL) and dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 9:1) to give the desired products **24a–d**.

*4.8.1. 3-Hydroxy-4-(1H-indol-3-yl)butan-2-one (actinopolymorphol B) (**24a**).* According to the general procedure, by using **26a** (0.450 g, 1.28 mmol) and K_2CO_3 (0.353 g, 2.56 mmol), **24a** (0.23 g, 89%) was obtained as a pale yellow oil: R_f 0.22 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=3406, 1709, 1618, 1457, 1425, 1355, 1244, 1093, 743 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.17 (s, 3H, C*H*$_3$CO), 3.10 (dd, *J*=15.0, 6.5 Hz, 1H, H-4), 3.29 (dd, *J*=15.0, 3.0 Hz, 1H, H-4), 3.48 (br s, 1H, OH), 4.50 (br s, 1H, H-3), 7.04 (s, 1H, H-2′), 7.12 (br t, *J*=8.0 Hz, 1H, H-5′), 7.18 (br t, *J*=8.0 Hz, 1H, H-6′), 7.31 (d, *J*=8.0 Hz, 1H, H-7′), 7.62 (d, *J*=8.0 Hz, 1H, H-4′), 8.14 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=25.8 (*C*H$_3$CO), 29.5 (C-4), 77.1 (C-3), 110.2 (C-3′), 111.2 (C-7′), 118.6 (C-4′), 119.5 (C-5′), 122.1 (C-6′), 122.9 (C-2′), 127.4 (C-3a′), 136.1 (C-7a′), 209.9 (CH$_3$*C*O). MS (70 eV): *m*/*z* (%)=203 (M$^+$, 6), 160 (1), 144 (8), 131 (12), 130 (100), 103 (6), 77 (4). HRMS (EI) *m*/*z* [M$^+$] calcd for $C_{12}H_{13}NO_2$: 203.0946. Found: 203.0939.

*4.8.2. 4-(1-Allyl-1H-indol-3-yl)-3-hydroxybutan-2-one (**24b**).* According to the general procedure, by using **26b** (0.060 g, 0.15 mmol) and K_2CO_3 (0.043 g, 0.31 mmol), **24b** (0.026 g, 70%) was obtained as a pale yellow oil: R_f 0.44 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=3449, 2918, 1712, 1613, 1467, 1437, 1419, 1356, 1187, 1088, 1014, 991, 926, 741 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.19 (s, 3H, C*H*$_3$CO), 3.12 (ddd, *J*=15.0, 6.6, 0.5 Hz, 1H, H-4), 3.30 (ddd, *J*=15.0, 4.8, 0.9 Hz, 1H, H-4), 3.49 (br d, *J*=5.0 Hz, 1H, OH), 4.47–4.54 (m, 1H, H-3), 4.68 (dt, *J*=5.4, 1.7 Hz, 2H, H-1″), 5.04 (ddt, *J*=17.1, 2.9, 1.7 Hz, 1H, H-3″), 5.18 (ddt, *J*=10.2, 2.9, 1.7 Hz, 1H, H-3″), 5.96 (ddt, *J*=17.1, 10.2, 5.4 Hz, 1H, H-2″), 7.02 (s, 1H, H-2′), 7.12 (ddd, *J*=7.8, 6.9, 1.2 Hz, 1H, H-5′), 7.21 (ddd, *J*=8.1, 6.9, 1.2 Hz, 1H, H-6′), 7.29 (br d, *J*=8.1 Hz, 1H, H-7′), 7.62 (dd, *J*=7.8, 1.1 Hz, 1H, H-4′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.8 (*C*H$_3$CO), 29.5 (C-4), 48.7 (C-1″), 77.1 (C-3), 109.1 (C-3′), 109.7 (C-7′), 117.2 (C-3″), 118.8 (C-4′), 119.2 (C-5′), 121.7 (C-6′), 126.6 (C-2′), 128.0 (C-3a′), 133.3 (C-2″), 136.2 (C-7a′), 209.8 (CH$_3$*C*O). HRMS (EI) *m*/*z* [M$^+$–OH] calcd for $C_{15}H_{16}NO$: 226.1232. Found: 226.1231.

*4.8.3. 3-Hydroxy-4-(1-(prop-2-yn-1-yl)-1H-indol-3-yl)butan-2-one (**24c**).* According to the general procedure, by using **26c** (0.290 g, 0.744 mmol) and K_2CO_3 (0.308 g, 2.23 mmol), **24c** (0.11 g, 61%) was obtained as a pale yellow oil: R_f 0.32 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=3462, 3282, 1711, 1466, 1356, 1185, 1086, 743 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.17 (s, 3H, C*H*$_3$CO), 2.37 (t, *J*=2.5 Hz, 1H, H-3″), 3.07 (ddd, *J*=15.0, 6.5, 1.0 Hz, 1H, H-4), 3.27 (ddd, *J*=15.0, 4.5, 1.0 Hz, 1H, H-4), 3.46 (d, *J*=5.0 Hz, 1H, OH), 4.45–4.49 (m, 1H, H-3), 4.79 (d, *J*=2.5 Hz, 1H, H-1″), 7.11 (s, 1H, H-2′), 7.14 (ddd, *J*=8.0, 7.0, 1.0 Hz, 1H, H-5′), 7.24 (ddd, *J*=8.5, 7.0, 1.5 Hz, 1H, H-6′), 7.35 (br d, *J*=8.5 Hz, 1H, H-7′), 7.62 (dt, *J*=8.0, 1.5 Hz, 1H, H-4′). ^{13}C NMR (125 MHz, $CDCl_3$): δ=25.8 (*C*H$_3$CO), 29.5 (C-4), 35.6 (C-1″), 73.5 (C-3″), 77.1 (C-3), 77.7 (C-2″), 109.4 (C-7′), 110.0 (C-3′), 119.0 (C-4′), 119.7 (C-5′), 122.1 (C-6′), 126.0 (C-2′), 128.4 (C-3a′), 135.9 (C-7a′), 209.6 (CH$_3$*C*O). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.71; H, 6.23; N, 5.86.

*4.8.4. 3-Hydroxy-4-(1-(3-methoxybenzyl)-1H-indol-3-yl)butan-2-one (**24d**).* According to the general procedure, by using **26d** (0.120 g, 0.254 mmol) and K_2CO_3 (0.070 g, 0.51 mmol), **24d** (0.078 g, 95%) was obtained as a pale yellow oil: R_f 0.38 (hexane/EtOAc, 7:3 (×2)). IR (film): $\overline{\nu}$=3459, 2921, 1711, 1601, 1489, 1465, 1436, 1353, 1262, 1150, 1085, 1044, 779, 741 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.16 (s, 3H, C*H*$_3$CO), 3.11 (dd, *J*=15.3, 6.6 Hz, 1H, H-4), 3.29 (dd, *J*=15.3, 4.8 Hz, 1H, H-4), 3.49 (br s, 1H, OH), 3.71 (s, 3H, C*H*$_3$O), 4.44–4.53 (m, 1H, H-3), 5.21 (s, 2H, H-1″), 6.60 (br s, 1H, H-2‴), 6.65 (br d, *J*=7.8 Hz, 1H, H-6‴), 6.77 (dd, *J*=8.3, 2.1 Hz, 1H, H-4‴), 7.04 (s, 1H, H-2′), 7.06–7.26 (m, 4H, H-5′, H-6′, H-7′, H-5‴), 7.63 (dd, *J*=6.6, 1.2 Hz, 1H, H-4′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.8 (*C*H$_3$CO), 29.5 (*C*H$_2$-4), 49.8 (C-1″), 55.1 (*C*H$_3$O), 77.1 (C-3), 109.4 (C-3′), 109.7 (C-7′), 112.4 (C-2‴), 112.7 (C-4‴), 118.8 (C-4′), 118.9 (C-6‴), 119.3 (C-5′), 121.9 (C-6′), 127.0 (C-2′), 128.1 (C-3a′), 129.7 (C-5‴), 136.4 (C-7a′), 139.0 (C-1‴), 159.8 (C-3‴), 209.7 (CH$_3$*C*O). HRMS (EI) *m*/*z* [M$^+$–OH] calcd for $C_{20}H_{21}NO_3$: 323.1521. Found: 323.1513.

4.9. 1-(1*H*-Indol-3-yl)-3-methylbutane-2,3-diol (tanakine) (25)

To a solution of **24a** (0.100 g, 0.49 mmol) in anhydrous THF (3 mL) at 0 °C a 3.0 M Et_2O solution of MeMgBr (0.293 g, 2.46 mmol)

was added, and the mixture stirred at 0 °C for 2 h. The mixture was extracted with EtOAc (2×10 mL), and washed with water (2×10 mL) and dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 1:1) to give **25** (0.064 g, 60%) as a pale yellow oil: R_f 0.26 (hexane/EtOAc, 1:1). IR (film): $\overline{\nu}$=3411, 2974, 1685, 1619, 1456, 1384, 1354, 1339, 1161, 1072, 1009, 742 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.32 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.09 (br s, 1H, OH), 2.33 (br s, 1H, OH), 2.75 (dd, J=14.5, 10.5 Hz, 1H, H-1), 3.07 (ddd, J=14.5, 2.5, 1.0 Hz, 1H, H-1), 3.73 (dd, J=10.5, 2.5 Hz, 1H, H-2), 7.09 (d, J=2.0 Hz, 1H, H-2′), 7.13 (td, J=7.5, 1.0 Hz, 1H, H-5′), 7.21 (td, J=7.5, 1.5 Hz, 1H, H-6′), 7.37 (d, J=7.5 Hz, 1H, H-7′), 7.60 (d, J=7.5 Hz, 1H, H-4′), 8.12 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=23.8 (CH_3), 26.6 (CH_3), 27.9 (C-1), 72.6 (C-3), 77.5 (C-2), 111.3 (C-7′), 112.4 (C-3′), 118.8 (C-4′), 119.5 (C-5′), 122.3 (C-6′), 122.8 (C-2′), 127.4 (C-3a′), 136.5 (C-7a′). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.25; H, 7.78; N, 6.38.

4.10. 5-((1*H*-Indol-3-yl)methyl)-4-methyl-3-(*p*-tolyl)oxazol-2(3*H*)-one (27a)

A mixture of **24a** (0.100 g, 0.49 mmol) and **9b** (0.157 g, 1.18 mmol) was irradiated with MW (CEM, 30 W) at 120 °C for 1.0 h. Afterward, the mixture was extracted with CH_2Cl_2 (5 mL) and filtered, and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 95:5) to give **27a** (0.102 g, 65%) as a pale brown solid: R_f 0.22 (hexane/EtOAc, 7:3); mp 193–194 °C. IR (film): $\overline{\nu}$=3310, 1743, 1699, 1515, 1386, 1169, 1039, 986, 819, 742 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.87 (s, 3H, CH_3-4), 2.36 (s, 3H, CH_3Ar), 3.89 (s, 2H, CH_2-5), 7.08 (d, J=2.0 Hz, 1H, H-2″), 7.11 (t, J=8.0 Hz, 1H, H-5″), 7.14 (d, J=8.1 Hz, 2H, H-2′), 7.17 (t, J=8.0 Hz, 1H, H-6″), 7.23 (d, J=8.0 Hz, 2H, H-3′), 7.33 (d, J=8.0 Hz, 1H, H-7″), 7.58 (d, J=8.0 Hz, 1H, H-4″), 8.52 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=8.8 (CH_3-4), 20.9 (CH_3Ar), 21.1 (CH_2-5), 110.6 (C-3″), 111.5 (C-7″), 118.0 (C-4), 118.2 (C-4″), 119.4 (C-5″), 121.9 (C-6″), 122.9 (C-2″), 126.7 (C-3a″), 126.8 (C-2′), 130.0 (C-3′), 131.0 (C-1′), 134.8 (C-5), 136.2 (C-7a″), 138.4 (C-4′), 154.9 (C-2). HRMS (EI) m/z [M^+] calcd for $C_{20}H_{18}N_2O_2$: 318.1368. Found: 318.1375.

4.11. 3-(3-Chlorophenyl)-5-((1*H*-indol-3-yl)methyl)-4-methyloxazol-2(3*H*)-one (27b)

Following the method of preparation for **27a**, by using **24a** (0.200 g, 0.99 mmol) and **9c** (0.310 g, 1.97 mmol), **27b** (0.211 g, 63%) was obtained as a pale yellow oil: R_f 0.46 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=3332, 3058, 1746, 1702, 1593, 1483, 1433, 1382, 1183, 1097, 1007, 878, 766, 743 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.90 (s, 3H, CH_3-4), 3.89 (s, 2H, CH_2-5), 7.07 (d, J=2.5 Hz, 1H, H-2″), 7.12 (td, J=8.0, 1.0 Hz, 1H, H-5″), 7.13–7.65 (m, 1H, H-6′), 7.18 (td, J=8.0, 1.5 Hz, 1H, H-6″), 7.27–7.30 (m, 1H, Ar–H), 7.31–7.36 (m, 3H, Ar–H), 7.57 (d, J=8.0 Hz, 1H, H-4″), 8.43 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=8.8 (CH_3-4), 20.9 (CH_2-5), 110.4 (C-3″), 111.4 (C-7″), 117.6 (C-4), 118.2 (C-4″), 119.5 (C-5″), 122.1 (C-6″), 122.8 (C-2″), 125.1 (C-6′), 126.7 (C-3a″), 127.1 (Ar–H), 128.5 (Ar–H), 130.4 (Ar–H), 134.8 (Ar), 134.9 (Ar), 135.4 (C-5), 136.2 (C-7a″), 154.4 (C-2). Anal. Calcd for $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.37; H, 4.45; N, 8.26.

4.12. Methyl 5-((1*H*-indol-3-yl)methyl)-4-methyl-2-oxo-2,5-dihydrofuran-3-carboxylate (28a)

After stirring a mixture of dimethyl malonate (0.056 g, 0.43 mmol) and NaH (60%) (0.025 g, 0.63 mmol) in anhydrous THF (0.5 mL) at 0 °C for 10 min, a solution of **24a** (0.050 g, 0.25 mmol) in anhydrous THF (0.5 mL) was added dropwise, and the mixture was stirred at 0 °C for 1 h, then at room temperature for 1 h. Afterward, a 5% aqueous solution of HCl (2 mL) was added and extracted with EtOAc (2×10 mL), then the organic layer was washed with water (2×10 mL) and dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 9:1) to give **28a** (0.052 g, 74%) as a pale yellow solid: R_f 0.08 (hexane/EtOAc, 7:3); mp 179–181 °C. IR (film): $\overline{\nu}$=3361, 1766, 1717, 1457, 1436, 1358, 1336, 1232, 1096, 1053, 805, 745 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=2.37 (s, 3H, CH_3-4), 3.16 (ddd, J=15.5, 6.5, 0.5 Hz, 1H, CH_2-5), 3.43 (ddd, J=15.5, 4.5, 0.8 Hz, 1H, CH_2-5), 3.79 (s, 1H, CO_2CH_3), 5.15 (dd, J=6.5, 4.5 Hz, 1H, H-5), 7.08 (d, J=2.5 Hz, 1H, H-2′), 7.13 (ddd, J=8.0, 7.0, 1.0 Hz, 1H, H-5′), 7.18 (ddd, J=8.0, 7.0, 1.0 Hz, 1H, H-6′), 7.35 (dd, J=8.0, 1.0 Hz, 1H, H-7′), 7.56 (dd, J=7.0, 1.0 Hz, 1H, H-4′), 8.38 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.6 (CH_3-4), 27.4 (CH_2-5), 52.1 (CO_2CH_3), 82.8 (C-5), 107.9 (C-3′), 111.5 (C-7′), 118.1 (C-4′), 119.7 (C-5′), 119.8 (C-3), 122.1 (C-6′), 123.6 (C-2′), 127.0 (C-3a′), 135.9 (C-7a′), 161.7 (CO_2CH_3), 168.4 (C-2), 177.1 (C-4). HRMS (EI) m/z [M^+] calcd for $C_{16}H_{15}NO_4$: 285.1001. Found: 285.0998.

4.13. Methyl 4-methyl-2-oxo-5-((1*H*-pyrrol-2-yl)methyl)-2,5-dihydrofuran-3-carboxylate (28b)

Following the method of preparation for **28a**, by using **15d** (0.050 g, 0.33 mmol), NaH (60%) (0.033 g, 0.83 mmol), and dimethyl malonate (0.074 g, 0.56 mmol), **28b** (0.046 g, 60%) was obtained as a pale brown oil: R_f 0.30 (hexane/EtOAc, 1:1). IR (film): $\overline{\nu}$=3374, 1765, 1718, 1438, 1380, 1330, 1235, 1053, 805, 725 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=2.40 (s, 3H, CH_3-4), 2.96 (dd, J=15.5, 6.5 Hz, 1H, CH_2-5), 3.31 (dd, J=15.5, 3.5 Hz, 1H, CH_2-5), 3.85 (s, 1H, CO_2CH_3), 5.02 (dd, J=6.5, 3.5 Hz, 1H, H-5), 5.97 (br s, 1H, H-3′), 6.08 (dd, J=6.0, 3.0 Hz, 1H, H-4′), 6.69 (dd, J=3.0, 2.0 Hz, 1H, H-5′), 8.49 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.3 (CH_3-4), 30.2 (CH_2-5), 52.2 (CO_2CH_3), 82.8 (C-5), 107.6 (C-3′), 108.1 (C-4′), 118.4 (C-5′), 119.8 (C-3), 124.2 (C-2′), 161.5 (CO_2CH_3), 167.9 (C-2), 176.5 (C-4). HRMS (EI) m/z [M^+] calcd for $C_{12}H_{13}NO_4$: 235.0845. Found: 235.0837.

4.14. 3-(3-Chlorophenyl)-7a-((1*H*-indol-3-yl)methyl)-3a-methyl-3,3a,7,7a-tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (29)

A mixture of **27b** (0.030 g, 0.09 mmol) and **30a** (0.049 g, 0.90 mmol) was irradiated with MW (CEM, 200 W) at 100 °C for 18 h. The mixture was then extracted with CH_2Cl_2 (5 mL) and filtered, and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 95:5) to give **29** (0.02 g, 57%) as a pale yellow oil: R_f 0.36 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=3344, 2924, 1748, 1593, 1480, 1457, 1431, 1386, 1230, 1069, 1053, 788, 743, 726, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.62 (s, 3H, CH_3-3a), 2.31 (ddd, J=16.5, 3.0, 2.4 Hz, 1H, H-7), 2.44 (dd, J=16.5, 6.4 Hz, 1H, H-7), 3.25 (d, J=15.0 Hz, 1H, CH_2-7a), 3.37 (d, J=15.0 Hz, 1H, CH_2-7a), 5.00–5.14 (m, 1H, H-6), 6.51 (dd, J=5.4, 3.0 Hz, 1H, H-5), 7.13–7.25 (m, 3H, Ar–H), 7.27–7.35 (m, 4H, H-2″, Ar–H), 7.41 (br d, J=7.2 Hz, 1H, H-7″), 7.60 (br d, J=7.5 Hz, 1H, H-4″), 8.34 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.5 (CH_3-3a), 26.9 (C-7), 32.4 (CH_2-7a), 86.5 (C-7a), 94.5 (C-3a), 103.7 (C-6), 108.0 (C-3″), 111.4 (C-7″), 118.5 (C-4″), 119.8 (C-5″), 122.1 (C-6″), 124.6 (C-2″), 125.7 (ArH), 127.7 (ArH), 127.9 (C-3a″), 128.1 (ArH), 130.0 (ArH), 134.6 (Ar), 135.6 (Ar), 135.7 (C-7a″), 142.7 (C-5), 155.4 (C-2). HRMS (EI) m/z [M^+] calcd for $C_{22}H_{19}N_2O_3Cl$: 394.1084. Found: 394.1070.

4.15. General procedures for the preparation of 31a–d

Method A. A mixture of **10c** or **17a** (1.0 mol equiv) and **30b** (5.0 mol equiv) in anhydrous xylene (1 mL) was poured into

a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 and stirred at 160 °C for 72 h. The mixture was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 7:3) to give the desired product **31a** or **31c**, respectively.

Method B. A mixture of **10f** or **22e** (1.0 mol equiv) and **30b** (4.0 mol equiv) was poured into an MW tube (CEM, 120–200 W) and stirred at 100–120 °C for 12–16 h. The mixture was extracted with CH_2Cl_2 (5 mL) and filtered and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 9:1) to give the desired product **31b** or **31d**, respectively.

*4.15.1. 4-Methylene-5-(3-oxobutyl)-3-phenyl-5-(2,4,5-trimethoxybenzyl)oxazolidin-2-one (**31a**).* According to Method A of the general procedure, by using **10c** (0.100 g, 0.28 mmol) and **30b** (0.098 g, 1.40 mmol), **31a** (0.081 g, 68%) was obtained as a pale yellow solid: R_f 0.38 (hexane/EtOAc, 6:4); mp 130–132 °C. IR (CH_2Cl_2): $\overline{\nu}$=1766, 1712, 1678, 1513, 1459, 1399, 1208, 1035, 983, 853, 822, 760, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.16–2.24 (m, 1H, H-1″), 2.19 (s, 3H, CH_3CO), 2.26–2.37 (m, 1H, H-1″), 2.59 (ddd, J=17.6, 10.7, 5.2 Hz, 1H, H-2″), 2.72 (ddd, J=17.6, 10.7, 5.2 Hz, 1H, H-2″), 3.15 (s, 2H, CH_2–Ar), 3.77 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 3.90 (s, 3H, CH_3O), 4.09–4.12 (m, 2H, =CH_2), 6.54 (s, 1H, H-3‴), 6.85–6.91 (m, 3H, H-2′, H-6‴), 7.28–7.42 (m, 3H, H-3′, H-4′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=30.1 (CH_3CO), 32.5 (C-1″), 37.4 (C-2″), 38.1 (CH_2–Ar), 56.1 (CH_3O), 56.3 (CH_3O), 56.4 (CH_3O), 82.8 (=CH_2), 87.1 (C-5), 97.4 (C-3‴), 113.9 (C-1‴), 114.9 (C-6‴), 126.9 (C-2′), 128.4 (C-4′), 129.5 (C-3′), 133.6 (C-1′), 142.6 (C-5‴), 147.6 (C-4), 148.7 (C-4‴), 152.2 (C-2‴), 154.6 (C-2), 207.0 (CH$_3$CO). MS (70 eV): m/z (%)=425 (M^+, 1), 181 (100), 151 (24), 136 (10), 91 (16), 77 (17), 43 (24). Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.58; H, 6.26; N, 3.29.

*4.15.2. 3-(4-Chlorophenyl)-5-(4-methoxybenzyl)-4-methylene-5-(3-oxobutyl)oxazolidin-2-one (**31b**).* According to Method B of the general procedure, by using **10f** (0.050 g, 0.15 mmol) and **30b** (0.053 g, 0.76 mmol) and irradiating by MW (120 W) at 120 °C for 12 h, **31b** (0.049 g, 82%) was obtained as a pale yellow oil: R_f 0.24 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=2928, 1768, 1714, 1680, 1511, 1496, 1400, 1247, 1088, 1062, 1032, 983, 826, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.12–2.24 (m, 1H, H-1″), 2.20 (s, 3H, CH_3CO), 2.32 (ddd, J=14.9, 10.4, 5.7 Hz, 1H, H-1″), 2.58 (ddd, J=17.6, 10.4, 4.8 Hz, 1H, H-2″), 2.72 (ddd, J=17.6, 11.0, 5.7 Hz, 1H, H-2″), 2.82 (d, J=14.0 Hz, 1H, CH_2–Ar), 3.19 (d, J=14.0 Hz, 1H, CH_2–Ar), 3.79 (s, 3H, CH_3O), 4.11 (d, J=3.0 Hz, 1H, =CH_2), 4.14 (d, J=3.0 Hz, 1H, =CH_2), 6.66–6.72 (m, 2H, H-2′), 6.80–6.87 (m, 2H, H-3‴), 7.15–7.22 (m, 2H, H-2‴), 7.28–7.34 (m, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=30.1 (CH_3CO), 32.4 (C-1″), 37.4 (C-2″), 45.4 (CH_2–Ar), 55.2 (CH_3O), 82.8 (=CH_2), 86.8 (C-5), 113.6 (C-3‴), 125.5 (C-1‴), 128.3 (C-2′), 129.7 (C-3′), 131.6 (C-2‴), 131.8 (C-1′), 134.3 (C-4′), 146.9 (C-4), 154.1 (C-2), 159.0 (C-4‴), 207.0 (CH$_3$CO). Anal. Calcd for $C_{22}H_{22}NO_4Cl$: C, 66.08; H, 5.55; N, 3.50. Found: C, 66.10; H, 5.53; N, 3.55.

*4.15.3. 5-(Furan-2-ylmethyl)-4-methylene-5-(3-oxobutyl)-3-phenyloxazolidin-2-one (**31c**).* According to Method A of the general procedure, by using **17a** (0.085 g, 0.33 mmol) and **30b** (0.116 g, 1.65 mmol), **31c** (0.084 g, 78%) was obtained as a pale yellow solid: R_f 0.40 (hexane/EtOAc, 6:4); mp 89–90 °C. IR (CH_2Cl_2): $\overline{\nu}$=1768, 1711, 1678, 1500, 1400, 1353, 1144, 1250, 1065, 1010, 823, 755, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.10–2.21 (m, 1H, H-1″), 2.20 (s, 3H, CH_3CO), 2.23–2.35 (m, 1H, H-1″), 2.59 (ddd, J=17.8, 10.6, 5.3 Hz, 1H, H-2″), 2.73 (ddd, J=17.8, 10.6, 5.3 Hz, 1H, H-2″), 3.07 (d, J=15.1 Hz, 1H, CH_2–Ar), 3.27 (d, J=15.1 Hz, 1H, CH_2–Ar), 4.06 (d, J=3.0 Hz, 1H, =CH_2), 4.19 (d, J=3.0 Hz, 1H, =CH_2), 6.25 (br d, J=3.3 Hz, 1H, H-3‴), 6.35 (dd, J=3.3, 1.9 Hz, 1H, H-4‴), 7.03–7.08 (m, 2H, H-2′), 7.32–7.46 (m, 4H, H-3′, H-4′, H-5‴). ^{13}C NMR (75 MHz, $CDCl_3$): δ=30.1 (CH_3CO), 32.3 (C-1″), 37.2 (C-2″), 39.0 (CH_2–Ar), 83.0 (=CH_2), 85.3 (C-5), 109.2 (C-3‴), 110.6 (C-4‴), 127.0 (C-2′), 128.5 (C-4′), 130.0 (C-3′), 133.5 (C-1′), 142.2 (C-5‴), 147.1 (C-4), 148.7 (C-2‴), 154.1 (C-2), 207.0 (CH$_3$CO). MS (70 eV): m/z (%)=326 (M^++1, 1), 91 (13), 81 (26), 77 (62), 55 (20), 53 (45), 51 (44), 43 (100). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.89; H, 5.91; N, 4.30.

*4.15.4. 5-(((4-Chlorophenyl)thio)methyl)-4-methylene-5-(3-oxobutyl)-3-(p-tolyl)oxazolidin-2-one (**31d**).* According to Method B of the general procedure, by using **22e** (0.100 g, 0.29 mmol) and **30b** (0.812 g, 1.16 mmol) and irradiating by MW (200 W) at 100 °C for 16 h, **31d** (0.078 g, 65%) was obtained as a white solid: R_f 0.70 (hexane/EtOAc, 7:3); mp 75–77 °C. IR (film): $\overline{\nu}$=1766, 1714, 1680, 1659, 1516, 1476, 1402, 1201, 1144, 1093, 1074, 1010, 984, 818, 753 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=2.07–2.15 (m, 1H, H-1″), 2.17 (s, 3H, CH_3CO), 2.21–2.30 (m, 1H, H-1″), 2.40 (s, 3H, Ar–CH_3), 2.55 (ddd, J=17.6, 11.0, 5.0 Hz, 1H, H-2″), 2.66 (ddd, J=17.6, 11.0, 5.0 Hz, 1H, H-2″), 3.32 (d, J=14.5 Hz, 1H, CH_2–Ar), 3.35 (d, J=14.5 Hz, 1H, CH_2–Ar), 4.04 (d, J=3.0 Hz, 1H, =CH_2), 4.22 (d, J=3.0 Hz, 1H, =CH_2), 7.21–7.27 (m, 4H, H-2′, H-2‴), 7.27–7.31 (m, 2H, H-3′), 7.37–7.41 (m, 2H, H-3‴). ^{13}C NMR (125 MHz, $CDCl_3$): δ=21.2 (Ar–CH_3), 30.0 (CH_3CO), 32.4 (C-1″), 37.1 (C-2″), 46.2 (CH_2–Ar), 83.0 (=CH_2), 85.3 (C-5), 126.8 (C-2′), 129.2 (C-2‴), 130.3 (C-3′), 130.9 (C-1′), 132.5 (C-3‴), 133.3 (C-1‴), 134.2 (C-4‴), 138.7 (C-4′), 147.3 (C-4), 154.4 (C-2), 206.5 (CH$_3$CO). HRMS (EI) m/z [M^+] calcd for $C_{22}H_{22}NO_3SCl$: 415.1009. Found: 415.1020.

4.16. 3-(4-Chlorophenyl)-7a-(4-methoxybenzyl)-7,7a-dihydrobenzo[*d*]oxazol-2(3*H*)-one (32a)

A mixture of **10f** (0.050 g, 0.15 mmol) and **30a** (0.042 g, 0.75 mmol) was poured into an MW tube (CEM, 100 W) and stirred at 100 °C for 18 h. The mixture was extracted with CH_2Cl_2 (5 mL) and filtered, and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 95:5) to give **32a** (0.021 g, 38%) as a yellow oil: R_f 0.38 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=2925, 1776, 1672,1582, 1512, 1495, 1405, 1248, 1168, 1090, 1012, 827, 710 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=2.59 (dd, J=17.0, 6.0 Hz, 1H, H-7), 2.74 (dt, J=17.0, 3.0 Hz, 1H, H-7), 2.78 (d, J=14.0 Hz, 1H, CH_2-7a), 3.28 (d, J=14.0 Hz, 1H, CH_2-7a), 3.77 (s, 3H, CH_3O), 5.15 (d, J=5.0 Hz, 1H, H-4), 5.75 (ddd, J=9.0, 6.5, 2.5, 1H, H-6), 6.05 (ddd, J=9.0, 5.5, 3.5 Hz, 1H, H-5), 6.80–6.84 (m, 2H, H-3″), 6.84–6.87 (m, 2H, H-2′), 7.16–7.20 (m, 2H, H-2″), 7.28–7.31 (m, 2H, H-3′). ^{13}C NMR (125 MHz, $CDCl_3$): δ=33.3 (C-7), 38.9 (CH_2-7a), 55.3 (CH_3O), 83.3 (C-7a), 93.9 (C-4), 113.7 (C-3″), 119.8 (C-6), 124.4 (C-5), 126.4 (C-1″), 126.7 (C-2′), 129.4 (C-3′), 131.3 (C-2″), 132.1 (C-1′), 133.4 (C-4′), 140.4 (C-3a), 154.8 (C-2), 159.1 (C-4″). HRMS (EI) m/z [M^+–CO_2] calcd for $C_{21}H_{18}NO_3Cl$: 323.1077. Found: 323.1079.

4.17. 3a-Methyl-3-(*p*-tolyl)-7a-((*m*-tolylthio)methyl)-3,3a,7,7a-tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (33a)

A mixture of **22c** (0.119 g, 0.37 mmol) and **30a** (0.205 g, 3.70 mmol) was poured into an MW tube (CEM, 200 W) and stirred at 100 °C for 6 h. The mixture was extracted with CH_2Cl_2 (5 mL) and filtered, and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel (20 g/g crude, hexane/EtOAc, 95:5) to give **33a** (0.108 g, 78%) as a yellow oil: R_f 0.50 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$=2922, 1764, 1516, 1388, 1243, 1215, 1136, 1057, 1043, 981, 751, 735 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.55 (s, 3H, CH_3-3a), 2.32–2.39 (m, 1H, H-7), 2.34 (s, 3H, CH_3Ar), 2.37 (s, 3H, CH_3Ar), 2.66 (dd, J=16.5, 7.0 Hz, 1H, H-7), 3.31 (d, J=14.0 Hz, 1H, CH_2-7a), 3.51 (d, J=14.0 Hz, 1H, CH_2-7a), 5.19 (ddd, J=6.5, 5.5, 2.5 Hz, 1H, H-6), 6.52 (dd, J=5.5, 3.0 Hz, 1H, H-5), 7.06 (br

d, J=7.5 Hz, 1H, H-4″), 7.20 (t, J=7.5 Hz, 1H, H-5″), 7.21–7.24 (m, 2H, H-3′), 7.25–7.32 (m, 4H, H-2′, H-2″, H-6″). ^{13}C NMR (125 MHz, $CDCl_3$): δ=20.6 (CH_3-3a), 21.1 (CH_3-4′), 21.3 (CH_3-3″), 27.7 (C-7), 43.3 (CH_2-7a), 85.4 (C-7a), 94.0 (C-3a), 104.0 (C-6), 127.7 (C-2′), 128.0 (C-6″), 128.1 (C-4″), 129.0 (C-5″), 129.8 (C-3′), 131.5 (C-1′), 131.6 (C-2″), 135.7 (C-1″), 138.0 (C-4′), 139.0 (C-3″), 143.1 (C-5), 155.2 (C-2). HRMS (EI) m/z [M^+] calcd for $C_{22}H_{23}NO_3S$: 381.1399. Found: 381.1391.

4.18. 3-(4-Chlorophenyl)-7a-(4-methoxybenzyl)-3a,5-dimethyl-3,3a,7,7a-tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (33b)

Following the method of preparation for **33a**, by using **10f** (0.119 g, 0.36 mmol) and **30b** (0.126 g, 1.80 mmol) under MW (CEM, 100 W) irradiation at 100 °C for 18 h, **33b** (0.10 g, 70%) was obtained as a white solid: R_f 0.46 (hexane/EtOAc, 7:3); mp 105–106 °C. IR (film): $\bar{\nu}$=2953, 1759, 1716, 1612, 1513, 1496, 1382, 1249, 1203, 1179, 1110, 1091, 1057, 1033, 998, 983, 834, 763 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.57 (s, 3H, CH_3-3a), 1.81 (br d, J=1.5 Hz, 3H, CH_3-5), 2.12–2.26 (m, 2H, H-7), 2.90 (d, J=14.1 Hz, 1H, CH_2-7a), 3.15 (d, J=14.1 Hz, 1H, CH_2-7a), 3.80 (s, 1H, CH_3O), 4.71–4.77 (m, 1H, H-6), 6.84–6.90 (m, 2H, H-3″), 7.21–7.27 (m, 2H, H-2″), 7.28–7.33 (m, 2H, H-2′), 7.35–7.41 (m, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.4 (CH_3-5), 20.5 (CH_3-3a), 27.3 (C-7), 41.7 (CH_2-7a), 55.2 (CH_3O), 85.6 (C-7a), 94.5 (C-3a), 97.4 (C-6), 113.7 (C-3″), 126.1 (C-1″), 128.3 (C-2′), 129.2 (C-3′), 131.8 (C-2″), 133.3 (C-1′, C-4′), 150.4 (C-5), 155.1 (C-2), 158.8 (C-4″). HRMS (EI) m/z [M^+] calcd for $C_{22}H_{22}NO_4Cl$: 399.1237. Found: 399.1223.

4.19. Single-crystal X-ray crystallography[27]

Indole **27a** was obtained as colorless crystals (CH_2Cl_2). These were mounted on glass fibers. Crystallographic measurements were performed on an Oxford XCalibur diffractometer with Mo Kα radiation (λ=0.71073 Å; graphite monochromator) at room temperature. Two standard reflections were monitored periodically, showed no change during data collection. Unit cell parameters were obtained from a least-squares refinement. Intensities were corrected for Lorentz and polarization effects. No absorption correction was applied. Anisotropic temperature factors were introduced for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions and their atomic coordinates refined. Unit weights were used in the refinement. After being solved using SHELX-97,[28] the structure was visualized and plotted with the PLATON program package.[29] Data from **27a**: Formula: $C_{20}H_{18}N_2O_2$: molecular weight: 318.36; cryst syst.: orthorrombic; space group: *Pbca*; unit cell parameters: a, 9.2701(3), b, 18.8895(6), c, 19.4860(6) (Å); α, 90°, β, 90°, γ, 90°; temperature (K): 292(2); Z: 8; No. of reflections collected: 18,941; no. of independent reflections: 5703; no. of reflections observed: 3784; data collection range: 3.0<2θ<32.61°; R: 0.0314; GOF: 1.063.

Acknowledgements

We thank Miguel A. Caracas for his help in some experimental procedures, and Carlos Espinoza, Abigail I. Buendía, and Eder I. Martínez for their assistance in spectrometric measurements. We thank Bruce Allan Larsen for proofreading the manuscript. J.T. would like to acknowledge SIP-IPN (Grants 20110172, 20120830, 20130686, 20140858, and 20150917) and CONACYT (Grants 83446 and 178319) for financial support. D.Z.-Z., R.A., R.I.H.-B., and E.M.L. are grateful to CONACYT for graduate scholarships, and to the PIFI-IPN program for scholarship complements. D.Z.-Z. also thanks the Ludwig K. Hellweg Foundation for a partial scholarship. F.D. and J.T. are fellows of the EDI-IPN and COFAA-IPN programs.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.07.010.

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26. Web page: www.sevmexico.com.
27. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre (CCDC 1052474). The coordinates can be obtained, on request, from the Director Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
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