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Graphical Abstract

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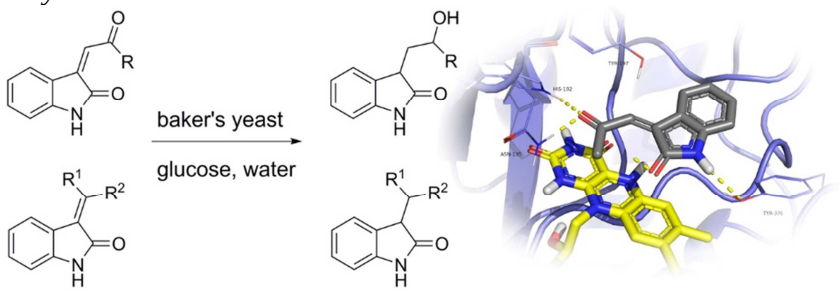

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ABSTRACT

3-Substituted oxindoles are very interesting molecules both for their potential biological activity and for their role as starting materials toward more complex oxindole-based structures. These molecules can be prepared by the reduction of a 3-ylidene oxindole precursor by classical metal-catalysed chemical reductions of the olefin. In this work we present a biocatalytic approach for the reduction of oxindole-based olefins using baker's yeast. All the substrates were efficiently reduced in high yields. When an α,β-unsaturated ketone was used, the corresponding saturated alcohol was obtained in high yield and ee. To further investigate the enzyme-substrate interactions a molecular docking study was also performed.

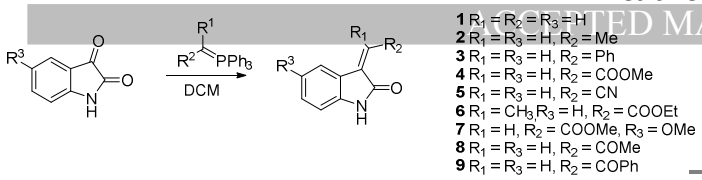
1. Introduction

Oxindoles are present in many natural and synthetic products showing pharmaceutical and biological activities.[1,2] Oxindole derivatives have been employed as anti-cancer,[3] antimicrobial,[4,5] anti-HIV,[6] and antimalarials.[7,8] In the past we demonstrated the utility of oxindoles as peptidomimetics capable of mimicking a β-turn structure.[9,10] The most common derivatives are 3,3-disubstituted oxindoles and 3-spirooxindoles containing a quaternary carbon centre and diverse functional groups. Spirooxindoles are also related to a series of alkaloids that were first isolated from plants of the Apocynaceae[11-13] and Rubiaceae[14-17] families.

The importance of isatin derivatives and their multiple applications has stimulated the interest of the researchers. In the last few years, lots of work has been devoted to finding an easy way to produce 3-substituted oxindoles, if possible with a controlled configuration at the stereocentre. Following our research activity in the preparation of oxindole-based compounds,[18-21] we became interested in the metal-free reduction of 3-yliden-oxindole derivatives by means of biocatalysis, in order to obtain 3-alkyl-oxindoles as possible substrates for further modifications. The use of biocatalysis offers the advantage of mild reaction conditions with limited use of organic solvents. Conversions are usually very high and when prochiral substrates are employed, chiral compounds can be obtained in high enantiomeric excesses. baker's yeast has been demonstrated to be an efficient catalyst for the reduction of activated olefins. This activity is due to the presence in this yeast of ene reductase (ER) enzymes of the OYE family. The use of baker's yeast for chemical transformations is encouraged by the fact that reactions are carried out in tap water, at room temperature and in the air in simple apparatus. The recovery of the products is easily realized by solvent extraction. An improvement of the recovery step is possible when the substrates are supported onto insoluble polystyrene resin, with the so-called Substrate Feeding Product Removal (SFPR) technique. In accordance with our experience in the use of biocatalytic systems for the reduction of activated olefins,[22-26] we decided to investigate the baker's yeast mediated reduction of olefins **1-13**. Very recently, a similar approach using *pseudomonas Monteilii* was reported,[27] thus confirming the urgent interest in this topic.[28] Nevertheless, *baker's yeast* is more simple to handle and scaling up to the preparation of grams of product is easily achievable. We selected differently substituted olefins in order to explore both the effect of different activating groups on the reactivity and the role of steric hindrance.

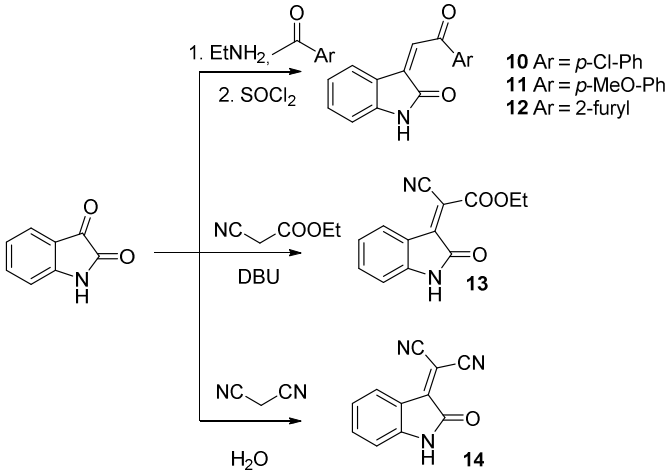
2. Results and discussion

The substrates were synthesized according to Schemes 1 and 2. Compounds **1-9** were prepared by standard Wittig olefination on commercial isatins.



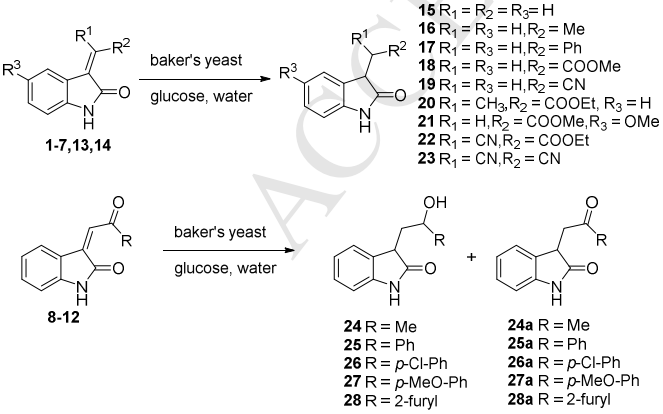
Scheme 1. Synthesis of **1-9** by Wittig olefination

Compounds **10-12** were produced by the reaction of isatin with the corresponding arylmethylketone with catalytic DEA (diethylamine) followed by dehydration with thionyl chloride. The reaction of isatin with ethylcyanoacetate and catalytic DBU (1,5-diazabiciclo(5.4.0)undec-5-ene) afforded compound **13**, while grinding isatin with malononitrile and a substechiometric equivalent of water afforded derivative **14**.



Scheme 2. Synthesis of compounds **10-14** by condensation reactions on isatin.

The olefins were then submitted to reaction with dried yeast (Sigma-Aldrich) in tap water (150 g/L) in the presence of D-glucose (15.0 g/L). Substrates were added at a concentration of 3 g/L. Reaction were usually carried on the 100 mg scale of olefin. If necessary, some drops of ethanol were added to facilitate the dissolution of substrates. The mixtures were incubated at 35 °C for 72 h in an orbital shaker. The same conditions were applied when using the SFPR technique. In this case the resin (Amberlite XAD 1180-N) was loaded in a 1:20 substrate/resin ratio.



Scheme 3. Reaction of olefins **1-14** with baker's yeast.

Results are reported in Table 1. Products **15-23** were isolated from substrates **1-7**, **13**, **14** after chromatographic purification. As expected when unsaturated ketones **8-12** were employed, the corresponding saturated alcohols **24-28** were isolated as the major product, due to the concomitant activity of the alcohol dehydrogenase enzymes (ADH) which are present in the baker's yeast. The saturated ketones **24a-28a** were also obtained in a 2-6% yield, according to ^{1}H NMR analysis of the crude reaction mixture (products were not isolated).

Substrate	product	Yield[a]	Yield[b]	dr[c]
1	**15**	71%	83%	-
2	**16**	72%	77%	-
3	**17**	58%	79%	-
4	**18**	68%	88%	-
5	**19**	69%	78%	-
6	**20**	<5%[c]	<5%[c]	60:40
7	**21**	67%	75%	-
8	**24**	66%	82%	55:45
9	**25**	62%	70%	50:50
10	**26**	59%	81%	52:48
11	**27**	44%	69%	57:43
12	**28**	51%	77%	51:49
13	**22**	-	-	-
14	**23**	14%[c]	13%[c]	-

[a]Reaction performed without the use of resin. [b]With resin (SFPR). [c]Calculated from ^{1}H NMR and GC/MS analysis on the crude reaction mixture (product not isolated)

All the substrates could be efficiently transformed into products by baker's yeast. As expected, the use of the SFPR allowed isolation of the final products in significantly higher yields. The lowest yields were obtained with tetra-substituted olefins (**21-23**) probably due as a result of their increased steric hindrance. Despite the use of prochiral olefins, disappointingly no ee was detected after HPLC analysis of the product **18**. The preparation of enantioenriched 3-alkyl 2-oxindoles has been previously reported in the literature by means of different approaches.[29-33] In particular the reduction of 3-yliden-oxindoles catalysed by a chiral iridium complex was reported to proceed with ee up to 93%.[34] We reasoned that our results might be ascribable to an epimerisation of the newly formed stereogenic centre.[35] The chromatogram of the chiral HPLC separation of compound **18** is reported in Figure 1. The presence of a plateau between the peaks of the two enantiomers is characteristic of a racemization process of the product during the column elution,[36] due to epimerisation at the C3 position. To further investigate this aspect, the ^{1}H NMR spectrum of **18** was first recorded in $CDCl_3$. Upon addition of few drops of CD_3OD, after 24 h at room temperature we observed the complete disappearance of the C3 proton as a consequence of its exchange with deuterium (see Figure 1). These experiments proved the configurational lability of the C3 stereocenter due to the acidity of the hydrogen at C3.

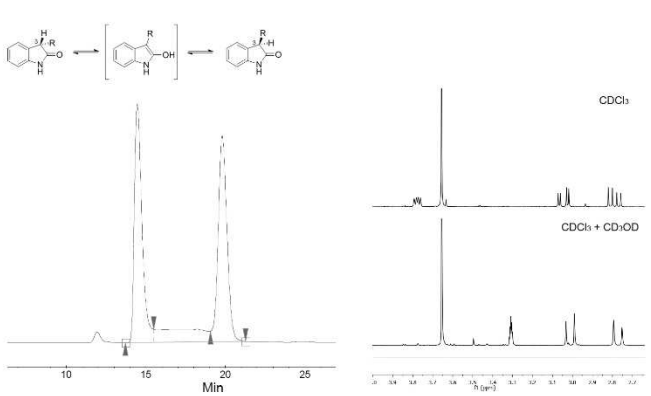
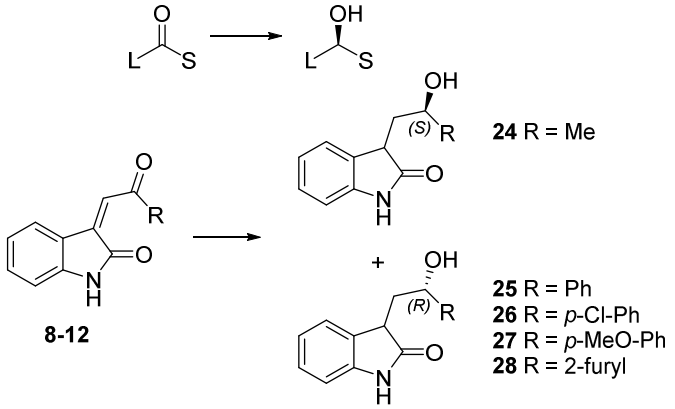


Figure 1. Racemisation process of compound **18**. Chiral HPLC (left image) and ^{1}H-NMR deuteration experiments are reported.

Alcohols **25-28** were obtained as a 1:1 mixture of diastereoisomers. In this case, as expected, the reduction of the carbonyl group by ADH enzymes proved to be very enantioselective, whereas the epimerization at C3 led to no diastereoisomeric excess. In fact, for representative compounds **24** and **25** an enantiomeric excess up to 98% could be measured by chiral HPLC. We did not determine the absolute configuration at the alcohol stereocenter of the major enantiomer, however, according to the Prelog's rule[37], we could suggest the stereochemical outcome proposed in Scheme 4. For compound **8**, bearing the small methyl group, the *S* configuration can be safely assigned. Whereas in the presence of an aryl substituent, the opposite result should be expected.



Scheme 4. Possible stereochemical outcome of the ADH-mediated reduction, according to the Prelog's rule.

According to the activation model for the reduction of activated olefins by baker's yeast, as observed for substrates **6, 13** and **14**, the reaction suffers from the steric hindrance around the carbon-carbon double bond. Despite the high steric demand introduced by the oxindole moiety, for trisubstituted olefins the conversions were good in all cases. Moreover, with the exception of compounds **1-3**, two different activating EWGs are present on the double bond, thus enabling different possible interaction modes with the ene-reductase enzymes. To better understand these aspects of the substrate-enzyme interaction, we performed a study on the docking modes of the oxindole-based olefins in an OYE 2 model receptor. Though in baker's yeast different ene-reductase enzymes are present, the activation of substrates and hydride transfer from FMNH occur in similar way.[38,39] Moreover, according to our experience, the stereochemical outcome of the reduction by baker yeast or isolate enzymes is in most cases the same. [24] The homology model of the OYE 2 enzyme was created with the YASARA software and docking experiments were carried out with Autodock 4.2. According to the mechanism, in our model the substrate is activated by interaction of the EWG of the olefin with His192 and Asp195 through hydrogen bonds. The olefin is then reduced by 1,4-addition of hydride from FMNH, followed by protonation from Tyr197 (Figure 2).

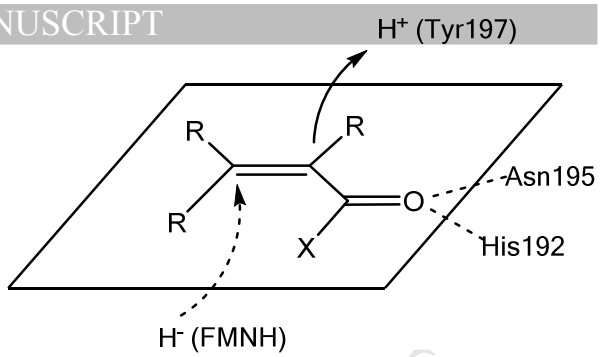


Figure 2. Activation mode for the OYE reduction of olefins.

We investigated the binding modes for representative compounds **1, 4, 8,** and **14**. The lowest energy poses for methylester **4** and olefin **1** are reported in Figure 3. For **4** a normal mode of activation is realized, with the coordination of the carboxymethyl group to the active site. A further stabilizing hydrogen bond interaction between the oxindole nitrogen and Tyr376 is detected. A similar situation is present for compound **8** (see SI). In compound **1** the activation is still possible through the interaction with the oxindole carbonyl group, but with a different arrangement of the double bond, similar to the "flipped" mode previously reported with other substrates. This result is noteworthy, since the oxindole ring forces an *s-cis* conformation for the carbonyl-olefin system, a quite uncommon geometry for the OYE reduction of olefins. On the contrary, the docking pose obtained for **14** revealed a poor interaction of the substrate. In fact, only one of the two cyano residues can form a hydrogen bond and only with His192 (see SI). This result could be an explanation of the poor reactivity of this substrate.

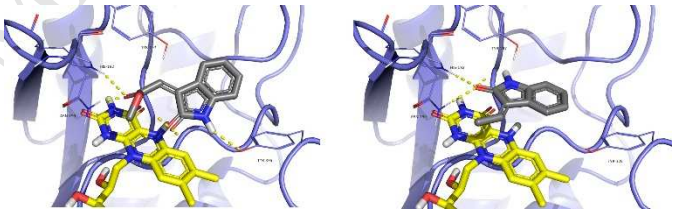


Figure 3. Comparison of the binding modes of **4** (left) and **1** (right) in the active site of OYE2. Reducing cofactor FMNH is depicted in yellow.

3. Conclusions

In this work we demonstrated the utility of baker's yeast for the reduction of 3-ylidene oxindoles, aimed at the preparation of 3-substituted oxindoles. Good results were obtained even with highly hindered tri-substituted olefins bearing different functional groups. No enantioselection was achieved, due to the easy racemization of the reduced product in the reaction medium. When a keto group was present on the double bond, the diastereoisomeric saturated alcohols were obtained with very high enantiomeric excess.

4. Experimental Section

4.1. General

All solvents were distilled and dried over sodium or calcium chloride, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light (254 nm) or by treatment with 1% aqueous $KMnO_4$ solution. Products were purified by flash

chromatography on silica gel 60 (230 - 400 mesh). GC–MS analyses were performed by using an HP-5 MS column (30 m × 0.25 mm × 0.25 µm, Agilent). The following temperature program was employed: 60 °C (1 min)/6 °C min^{-1}/150 °C (1 min)/12 °C min^{-1}/280 °C (5 min). The enantiomeric excess was determined by HPLC on a Chiralpak AD column (eluent 9:1, hexane : isopropanol, flow rate 0,75 mL/min). NMR spectra were recorded with a Bruker Avance 400 MHz spectrometer. Chemical shifts (δ) are expressed in ppm relative to TMS at δ = 0 ppm for ^{1}H NMR and relative to $CDCl_3$ at δ = 77.16 ppm for ^{13}C NMR. Some ^{13}C NMR spectra have been recorded using the APT pulse sequence; the signals of CH and CH_3 are positive while CH_2 and quarternary carbons are negative. FT-IR spectra were recorded in the ATR mode on an Agilent instrument. HR-EI mass spectra were measured on VG 70–70 EQ–HF instrument equipped with its standard sources.

*4.2. General procedure for the synthesis of compounds **1-3** by Wittig olefination.*

To a solution of the phosphonium salt (10.0 mmol) in THF (70 mL) at 0°C, *t*-BuOK (1.26 g, 11.22 mmol) was added. The reaction was stirred for 1 h to allow the formation of the ylide. A solution of isatin (10.0 mmol) in THF (70 mL) was added slowly to the reaction mixture at 0°C. The resulting solution was stirred for 15 h at rt. The reaction was poured into saturated ammonium chloride (70 mL) at 0° C. The compound was extracted with DCM (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 2:8 EtOAc/hexane.

*4.3. General procedure for the synthesis of compounds **4-9** by Wittig olefination.*

To a solution of isatin (0.04 mol) in DCM (150 mL), the corresponding previously prepared stabilized ylide (0.04 mol) was added. The mixture was stirred for 24 h at rt. The solution was concentrated under reduced pressure and the residue purified by silica gel column chromatography eluting with 2:8 EtOAc/hexane. to provide the product as a solid.

*4.4. General procedure for the synthesis of compounds **10-12***

Isatin (6 mmol) and the methylketone (6 mmol) were dissolved in 20 mL of ethanol. Diethylamine (124 µL, 1.2 mmol) was added and the reaction mixture was stirred at rt for 48 h. The solvent was removed under reduced pressure and the residue was dissolved in 15 mL of DCM and $SOCl_2$ (290 µL, 4 mmol) was added. After 2 h at rt the solvent was removed under reduced pressure and the crude product was recrystallized from ethanol to afford the pure compound.

Compounds **13**[40] and **14**[41] were prepared according to literature. Spectroscopic data for compounds **1**,[42] **2**,[43] **3**,[44] **4**,[45] **5**,[46] **8**,[47] **9**,[48] were in agreement with literature values.

*4.5. Spectroscopic data for compounds **1-14**:*

*4.5.1. 3-methyleneindolin-2-one**1***

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.48 (d, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.39 (s, 1H), 6.12 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0, 142.3, 134.9, 127.7, 125.4, 124.6, 122.4, 120.1, 110.3.

*4.5.2. 3-ethylideneindolin-2-one**2***

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5, 1H), 7.09 (q, *J* = 6.4 Hz, 1H), 6.93 (t, *J* = 7.4, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 2.32 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.3, 140.2, 137.0, 128.3, 127.7, 123.3, 120.8, 119.3, 109.3, 13.7

*4.5.3. 3-benzylideneindolin-2-one**3***

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29-8.25 (m, 2H), 7.78 (s, 1H), 7.57-7.51 (m, 2H), 7.48-7.42(m, 3H), 7.22 (t, 1H, *J* = 8.0 Hz), 7.04 (d, 1H, *J* = 7.6 Hz), 6.84 (t, 1H, *J* = 8.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 139.5, 137.6, 133.7, 132.0, 130.6, 128.9, 128.3, 126.1, 125.3, 121.8, 119.3, 109.4.

*4.5.4. methyl-2-(2-oxoindolin-3-ylidene)acetate**4***

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H) , 8.53 (s, 1H), 7.28-7.36 (m, 1H), 7.00-7.09 (m, 1H), 6.84-6.88 (m, 2H), 3.8 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 165.9, 150.8, 132.6, 130.5, 129.2, 122.9, 122.0, 110.0, 52.1.

*4.5.5. 2-(2-oxoindolin-3-ylidene)acetonitrile**5***

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.42 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.10 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.53 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.9, 145.6, 144.7, 134.8, 124.9, 123.3, 120.3, 117.8, 111.9, 98.6.

*4.5.6. Ethyl (Z)-2-(2-oxoindolin-3-ylidene)propanoate **6**.*

Yellow solid. m.p. 180°C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.58 – 7.44 (m, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.02 (td, *J* = 7.7, 1.1 Hz, 1H), 6.85 (dt, *J* = 7.7, 0.8 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.3, 141.0, 140.4, 129.8, 125.2, 122.9, 122.0, 121.1, 110.0, 61.8, 16.4, 14.1. ν_{max}(ATR) 3079, 1726, 1703, 1613, 1467, 1113. HRMS (EI): calculated for $C_{13}H_{13}NO_3$: 231.0895; found 231.0894.

*4.5.7. Methyl (Z)-2-(5-methoxy-2-oxoindolin-3-ylidene)acetate **7***

Brown solid. m.p. 184°C ^{1}H NMR (400 MHz, CD_3CN) δ 8.37 (s, 1H), 8.10 (d, *J* = 2.7 Hz, 1H), 6.94 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.68 (s, 1H), 3.84 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, CD_3CN) δ 178.4, 172.1, 156.1, 136.4, 131.1, 113.1, 111.7, 110.2, 52.0, 42.9, 34.4, 14.2. ν_{max}(ATR) 3175, 2922, 1702, 1437, 1207. HRMS (EI): calculated for $C_{12}H_{11}NO_4$: 233.0688; found 233.0692.

*4.5.8. (Z)-3-(2-oxopropylidene)indolin-2-one**8***

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 7.8 Hz, 1H), 7.84 (s, 1H), 7.32 (td, *J* = 7.7, 1.3 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.09 – 6.95 (m, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 2.47 (d, *J* = 1.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.55, 169.95, 155.76, 143.50, 135.63, 128.63, 127.87, 123.09, 120.75, 133.17, 32.35.

*4.5.9. (Z)-3-(2-oxo-2-phenylethylidene)indolin-2-one**9***

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dt, *J* = 7.8, 0.6 Hz, 1H), 8.18 – 8.05 (m, 2H), 7.89 (s, 1H), 7.71 – 7.63 (m, 1H), 7.59 – 7.50 (m, 2H), 7.36 – 7.30 (m, 1H), 7.04 (td, *J* = 7.7, 1.0 Hz, 1H), 6.87 (dd, *J* = 7.8, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.1, 169.4, 143.3, 137.6, 136.7, 133.8, 132.7, 128.9, 128.8, 128.0, 126.5, 122.9, 120.7, 110.1.

*4.5.10. (Z)-3-(2-(4-chlorophenyl)-2-oxoethylidene)indolin-2-one **10**.*

Red solid. m.p. 225°C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.09 (d, *J* = 8.6 Hz, 2H), 8.07 – 8.03 (m, 1H), 7.69 (s, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.36 (td, *J* = 7.7, 1.3 Hz, 1H), 6.97 (td, *J* = 7.7, 1.1 Hz, 1H), 6.89 (dt, *J* = 7.8, 0.8 Hz, 1H). ^{13}C

NMR (101 MHz, DMSO-d_6) δ 190.6, 168.6, 145.5, 139.4, 137.3, 136.2, 133.6, 131.0, 129.7, 127.3, 125.8, 122.2, 120.4, 110.9. ν_{max}(ATR) 3146, 3085, 1715, 1495, 1327. HRMS (EI): calculated for $C_{16}H_{10}ClNO_2$: 283.0400; found 283.0404.

4.5.11. (Z)-3-(2-(4-methoxyphenyl)-2-oxoethylidene)indolin-2-one ***11***.

Brown solid. m.p. 197°C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 8.06 (d, *J* = 8.9 Hz, 2H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.69 (s, 1H), 7.33 (td, *J* = 7.7, 1.3 Hz, 1H), 7.13 (d, *J* = 8.9 Hz, 2H), 6.94 (td, *J* = 7.7, 1.3 Hz, 1H), 6.88 (dt, *J* = 7.8, 0.8 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 190.2, 168.7, 164.4, 145.1, 136.0, 133.0, 131.6, 130.4, 127.1, 127.0, 122.1, 120.5, 114.9, 110.8, 56.2. ν_{max}(ATR) 3147, 1706, 1603, 1457, 1010. HRMS (EI): calculated for $C_{17}H_{13}NO_3$: 279.0895; found 279.0893.

4.5.12. (Z)-3-(2-(furan-2-yl)-2-oxoethylidene)indolin-2-one ***12***.

Red solid. m.p. 188°C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 1.0 Hz, 1H), 7.71 (dd, *J* = 3.7, 1.0 Hz, 1H), 7.59 (s, 1H), 7.39 (td, *J* = 7.7, 1.0 Hz, 1H), 7.03 (dd, *J* = 7.6, 1.1 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.83 (dd, *J* = 3.7, 1.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 177.2, 168.7, 153.8, 149.6, 145.8, 133.2, 128.6, 128.0, 126.0, 124.2, 122.3, 120.6, 113.9, 110.8. ν_{max}(ATR) 3186, 2921, 1706, 1458, 1328. HRMS (EI): calculated for $C_{14}H_9NO_3$: 239.0582; found 239.0581.

4.5.13. ethyl-2-cyano-2-(2-oxoindolin-3-ylidene)acetate ***13***

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.0 Hz, 1H), 7.56 (s, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.71 (t, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 164.5, 163.8, 135.9, 127.9, 126.8, 126.4, 124.0, 120.3, 117.2, 106.3, 59.1, 13.7.

4.5.14. 2-(2-oxoindolin-3-ylidene)malononitrile ***14***

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.14 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.7, 151.5, 147.4, 138.7, 126.7, 123.8, 119.6, 114.0, 112.5, 112.4, 81.5.

4.6. General procedure for the baker's yeast reduction of olefins

To a mixture of commercial fresh or freeze-dried baker's yeast (Sigma) (7.5 g) in tap water (50 mL) at 40°C, D-glucose (0.75g, 4.17 mmol) was added. The substrate (100 mg) was added and the flask was placed for 2 d in a termo-shaker. The mixture was then filtered on a celite pad and washed twice with water (50 mL) and once with EtOAc (50 mL). The aqueous was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 4:6 EtOAc/hexane to give the product.

4.7. Spectroscopic data for compounds ***15-17***,[48] *and* ***18***, ***19***[49] *were in agreement with literature values.*

4.7.1. 3-methylindolin-2-one ***15***

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (1H, br s), 7.21 (2H, td, *J* = 7.4, 0.8 Hz), 7.03 (1H, td, *J* = 7.5, 1.0 Hz), 6.93 (1H, d, *J* = 7.5 Hz), 3.47 (1H, q, *J* = 7.7 Hz), 1.51 (3H, d, *J* = 7.7 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.4, 141.2, 131.2, 127.9, 123.8, 122.3, 109.7, 41.0, 15.2.

4.7.2. 3-ethylindolin-2-one ***16***

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.23 (d, 1H, *J* = 7.7 Hz), 7.22 (t, 1H, *J* = 7.7 Hz), 7.04 (t, 1H, *J* = 7.7 Hz), 6.88 (1H, d, *J* = 7.7 Hz), 3.46 (1H, t, *J* = 5.8 Hz), 2.04 (m, 2H), 0.93 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 141.6, 129.5, 127.8, 124.1, 122.2, 109.5, 47.0, 23.5, 9.9

4.7.3. 3-benzylindolin-2-one ***17***

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (1H, br s), 7.29-7.15 (6H, m), 7.03 (1H, td, *J* = 7.5, 1.0 Hz), 6.92-6.86 (2H, m); 6.75 (1H, d, *J* = 7.4 Hz), 3.77 (1H, dd, *J* = 9.3, 4.5 Hz), 3.52 (1H, dd, *J* = 13.7, 4.6 Hz), 2.95 (1H, dd, *J* = 13.7, 9.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 141.5, 137.8, 129.4, 129.0, 128.3, 127.9, 126.6, 124.7, 121.9, 109.8, 47.6, 36.6.

4.7.4. methyl 2-(2-oxoindolin-3-yl)acetate ***18***

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 7.24-7.20 (m, 2H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 3.82 (dd, *J* = 4.8, 8.0 Hz, 1H), 3.70 (s, 3H), 3.09 (dd, *J* = 4.4, 16.8 Hz, 1H), 2.84 (dd, *J* = 8.0, 16.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.2, 171.6, 141.5, 128.6, 128.3, 124.1, 122.5, 109.9, 52.1, 42.3, 34.5

4.7.5. 2-(2-oxoindolin-3-yl)acetonitrile ***19***

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (1H, s,), 7.39 (1H, d, *J*=7.4 Hz), 7.24 (1H, t, *J*=7.7 Hz), 7.01 (1H, t, *J*=7.5 Hz), 6.88 (1H, d, *J*=7.7 Hz), 3.82 (1H, t, *J*=5.9 Hz), 3.20 (1H, dd, *J*=17.2, 5.8 Hz), 3.06 (1H, dd, *J*=17.2, 5.9 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.4, 142.8, 128.6, 127.1, 124.2, 121.6, 118.2, 109.6, 41.3, 17.6.

4.7.6. methyl 2-(5-methoxy-2-oxoindolin-3-yl)acetate ***21***

Orange solid. m.p. decompose. ^{1}H NMR (400 MHz, CD_3CN) δ 8.31 (s, 1H), 6.90 – 6.70 (m, 3H), 3.76 (s, 3H), 3.70 – 3.65 (m, 1H), 3.64 (s, 3H), 3.00 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.86 (dd, *J* = 17.0, 6.9 Hz, 1H). ^{13}C NMR (101 MHz, CD_3CN) δ 171.5, 166.6, 155.9, 139.4, 138.9, 123.1, 121.7, 119.2, 114.6, 111.3, 56.0, 52.5. ν_{max}(ATR) 3263, 2924, 1711, 1487, 1203. HRMS (EI): calculated for $C_{12}H_{13}NO_4$: 235.0845; found 235.0841.

4.7.7. 3-(2-hydroxypropyl)indolin-2-one ***24***. *mixture of two diastereoisomers.*

Yellow solid. m.p. 84°C (decompose) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 0.5H, *diast A*), 8.80 (s, 0.5H, *diast B*), 7.25 – 7.13 (m, 2H), 7.09 – 6.98 (m, 1H), 6.93 – 6.84 (m, 1H), 4.24 (td, *J* = 6.4, 3.0 Hz, 0.5H, *diast A*), 4.17 – 4.08 (m, 0.5H, *diast B*), 3.73 – 3.60 (m, 1H), 2.89 (d, *J* = 6.3 Hz, 1H), 2.16 (ddd, *J* = 14.0, 9.1, 4.7 Hz, 0.5H, *diast A*), 2.04 – 1.82 (m, 1.5H), 1.30 (d, *J* = 6.2 Hz, 1.5H, *diast A*), 1.27 (d, *J* = 6.3 Hz, 1.5H, *diast B*). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 181.7 and 181.6, 141.3 and 141.1, 129.4 and 129.3, 127.1 and 126.8, 123.9 and 123.8, 122.7 and 122.5, 110.1 and 109.9, 64.4 and 64.2, 44.7 and 44.2, 41.1 and 40.0, 23.6 and 23.3. ν_{max}(ATR) 3437, 2925, 2987, 1470, 1137. HRMS (EI): calculated for $C_{11}H_{13}NO_2$: 191.0946; found 191.0944.

4.7.8. 3-(2-hydroxy-2-phenylethyl)indolin-2-one ***25***.

Yellow solid. m.p. 104°C mixture of two diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 0.5H, *diast A*), 8.90 (s, 0.5H, *diast B*), 7.38 – 6.98 (m, 8H), 6.91 – 6.80 (m, 1H), 5.12 – 5.03 (m, 1H), 4.74 (s, 0.5H, *diast A*), 4.17 (s, 0.5H, *diast B*), 3.69 (t, *J* = 7.0 Hz, 0.5H, *diast A*), 3.59 (dd, *J* = 9.3, 3.9 Hz, 0.5H, *diast B*), 2.40 (ddd, *J* = 14.6, 8.1, 4.0 Hz, 0.5H, *diast A*), 2.27 – 2.10 (m, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.7 and 181.6, 142.8 and 142.6, 141.3 and 141.1, 133.2 and 133.0, 129.4 and 129.3, 128.8 - 128.6 (2C), 128.3 and 128.1, 127.3 and 127.0 (2C), 124.0 and 123.8, 122.9 and 122.7, 110.2 and 110.1, 72.8 and 70.5, 45.3 and 43.0, 40.3 and 39.0. ν_{max}(ATR) 3250, 1698,

1620, 1470. HRMS (EI): calculated for $C_{16}H_{15}NO_2$: 253.1103; found 253.1106.

4.7.9. 3-(2-(4-chlorophenyl)-2-hydroxyethyl)indolin-2-one ***26****.*

Yellow solid. m.p. 125°C mixture of two diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 0.5H, *diast A*), 8.90 (s, 0.5H, *diast B*), 7.36 – 7.25 (m, 4H, *diast A+ diast B*), 7.22 – 7.10 (m, 2H, *diast A+ diast B*), 7.06 – 6.96 (m, 1H, *diast A+ diast B*), 6.90 – 6.83 (m, 1H, *diast A+ diast B*), 5.15 – 5.01 (m, *J* = 7.8, 5.4 Hz, 1H, *diast A+ diast B*), 4.74 (s, 0.5H, *diast A*), 4.17 (s, 0.5H, *diast B*), 3.69 (t, *J* = 6.9 Hz, 0.5H, *diast A*), 3.59 (dd, *J* = 9.3, 3.9 Hz, 0.5H, *diast B*), 2.40 (ddd, *J* = 14.6, 8.1, 4.0 Hz, 0.5H, *diast A*), 2.26 – 2.10 (m, 1.5H, *diast A+ diast B*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.7 and 181.6, 142.8 and 142.6, 141.3 and 141.1, 133.2 and 133.0, 129.4 and 129.3, 128.6 and 128.6 (2C), 128.3 and 128.1, 127.3 and 127.0 (2C), 124.0 and 123.8, 122.9 and 122.7, 110.2 and 110.1, 72.8 and 70.5, 45.3 and 43.0, 40.3 and 39.0. ν_{max}(ATR) 3195, 1687, 1613, 1510, 1469, 1247. HRMS (EI): calculated for $C_{16}H_{14}ClNO_2$: 287.0713; found 287.0715.

4.7.10. 3-(2-hydroxy-2-(4-methoxyphenyl)ethyl)indolin-2-one ***27****.*

Yellow solid. m.p. 115°C mixture of two diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 0.5H, *diast A*), 9.13 (s, 0.5H, *diast B*), 7.26 – 7.19 (m, 2H), 7.15 – 7.10 (m, 1H), 7.09 – 7.01 (m, 2H), 6.94 – 6.88 (m, 1H), 6.78 (dd, *J* = 7.5, 5.8 Hz, 2H), 5.01 – 4.94 (m, 1H), 4.38 (bs, 0.5H, *diast A*), 3.94 (d, *J* = 5.8 Hz, 0.5H, *diast B*), 3.68 (s, 1.5H, *diast A*), 3.65 (s, 1.5H, *diast B*), 3.61 – 3.55 (m, 0.5H, *diast A*), 3.52 (dd, *J* = 8.9, 4.3 Hz, 0.5H, *diast B*), 2.39 – 2.29 (m, 0.5H, *diast A*), 2.22 – 2.01 (m, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.8 and 181.6, 159.1 and 158.9, 141.6 and 141.4, 136.5 and 136.3, 129.7 and 129.6, 128.1 and 127.9, 127.2 and 126.9 (2C), 124.1 and 123.8, 122.6 and 122.4, 113.9 and 113.8 (2C), 110.1 and 110.0, 72.7 and 70.6, 55.3 and 55.2, 45.1 and 43.1, 40.3 and 39.2. HRMS (EI): calculated for $C_{17}H_{17}NO_3$: 283.1208; found 283.1205.

4.7.11. 3-(2-(furan-2-yl)-2-hydroxyethyl)indolin-2-one ***28****.*

Yellow solid. m.p. 101°C (decompose) mixture of two diastereoisomers.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 0.5H, *diast A*), 8.63 (s, 0.5H, *diast B*), 7.40 – 7.34 (m, 1H), 7.30 – 7.23 (m, 1H), 7.24 – 7.17 (m, 1H), 7.05 (ddd, *J* = 7.7, 6.9, 1.0 Hz, 1H), 6.90 (t, *J* = 7.2 Hz, 1H), 6.36 – 6.29 (m, 2H), 5.17 (dd, *J* = 8.8, 4.6 Hz, 0.5H, *diast A*), 5.11 (dd, *J* = 8.0, 3.8 Hz, 0.5H, *diast B*), 4.23 (s, 0.5H, *diast A*), 3.93 (s, 0.5H, *diast B*), 3.74 – 3.68 (m, 0.5H, *diast A*), 3.65 (dd, *J* = 9.5, 4.0 Hz, 0.5H, *diast B*), 2.62 (ddd, *J* = 14.5, 7.9, 4.0 Hz, 0.5H, *diast A*), 2.45 – 2.26 (m, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.3 and 181.1, 156.2 and 156.1, 142.0 and 141.9, 141.2 and 141.0, 129.3, 128.2 and 128.1, 124.2 and 123.9, 122.8 and 122.7, 110.3 and 110.2, 110.0 and 109.9, 106.3 and 106.0, 66.9 and 65.6, 44.7 and 42.9, 36.7 and 35.7. ν_{max}(ATR) 3281, 1692, 1586, 1409, 1317. HRMS (EI): calculated for $C_{14}H_{13}NO_3$ 243.0895; found 243.0897.

4.8. Docking studies.

The selected ligands were first submitted to a Monte Carlo conformational search with the MMFF94 force field *in vacuo* with Spartan '08.[50] The obtained conformers were used for docking studies. The structure of OYE2 was obtained by homology modelling on the known crystal structure of OYE1 as obtained from the PDB database (1OYB.pdb) with the software YASARA.[51] The cofactor FMN was further converted to its reduced form $FMNH_2$. The obtained conformers were used for docking studies. Docking was performed using AutoDock5 using the default docking parameters supplied with AutoDock in the 'examples' subdirectory, and point charges initially assigned according to the AMBER03 force field, and then damped to mimic the less polar Gasteiger charges used to optimize the AutoDock scoring function. The setup was done with the YASARA molecular modeling program. For each ligands 50 Autodock LGA runs were executed. Results, were sorted by binding energy (more positive energies indicate stronger binding, and negative energies mean no binding). After clustering the 50 runs, the resulting complex conformations were originated (they all differ by at least 5.0 A heavy atom RMSD). Binding energy are reported in kcal/mol and predicted dissociation constant in pM units. Contacting receptor residues are also listed. The poses were then viewed using PyMOL.[52]

Appendix A. Supplementary data

Supplementary data (copy of NMR and IR spectra of new compounds, computational details) associated with this article can be found at

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