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Development of indanones and isatins as non-cytotoxic inhibitors of cholinesterases

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Abstract: A small library of indanone-amides and substituted isatin derivatives has been prepared; these compounds have been investigated for their ability to act as inhibitors for the enzymes acetyl- and butyrylcholinesterase (AChE, BChE). Several of them were moderate inhibitors for AChE and not cytotoxic for a variety of human tumor cell lines as well as for non-malignant mouse fibroblasts. In this library consisting of 49 derivatives, 5,7-dibromo-4-iodoisatin was shown to be a good mixed-type inhibitor for AChE (K_i = 2.52 ± 0.61 µM and $K_{i'}$ = 11.74 ± 1.31 µM) but this compound also acted as a dual inhibitor for BChE (K_i = 4.49 ± 0.32 µM and $K_{i'}$ = 6.56 ± 0.57 µM). Interestingly, *N*-hexyl-1-oxo-2,3-dihydro-1H-indene-2-carboxamide was cytotoxic especially for MCF-7 breast adenocarcinoma cells (EC_{50} = 4.28 ± 0.5 µM).

Keywords: acetylcholinesterase; butyrylcholinesterase; inhibitors; isatins; indanones.

1. Introduction

During the last decades, drugs have been developed for many human diseases. For some of them, however, there are currently only drugs available that alleviate by and large the symptoms, but they are unable to cure these diseases completely. One of those is Alzheimer's diseases (AD). In the therapy of AD, inhibitors of the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) have proved particularly effective as they slow down the course of the disease, and they allow the symptoms of the disease to be alleviated over a longer period of time. Thus, at least part of the quality of life can be preserved. Among others (as depicted in Fig.1), donepezil is a well-known AChE-inhibitor [1-3] that has been used for several years as medication for AD.

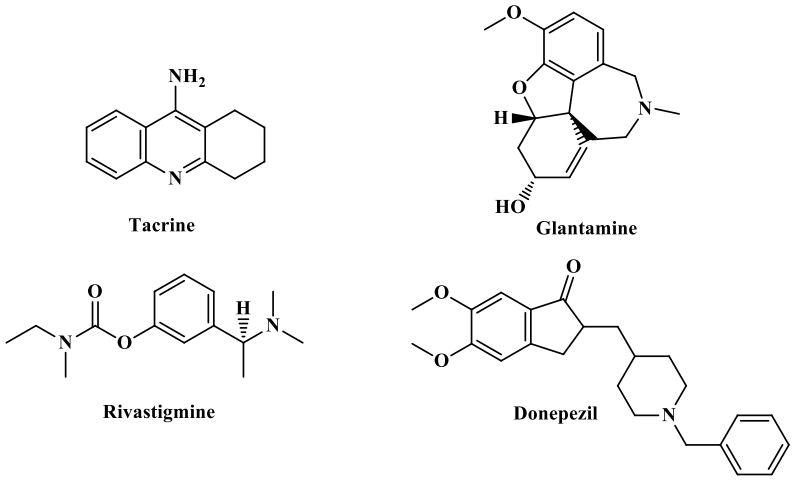

Figure 1. Today's most described drugs to alleviate AD

Despite some progress, there is still a need to find compounds being good dual inhibitors for acetylcholinesterase as well as for butyrylcholinesterase. In continuation of our previous

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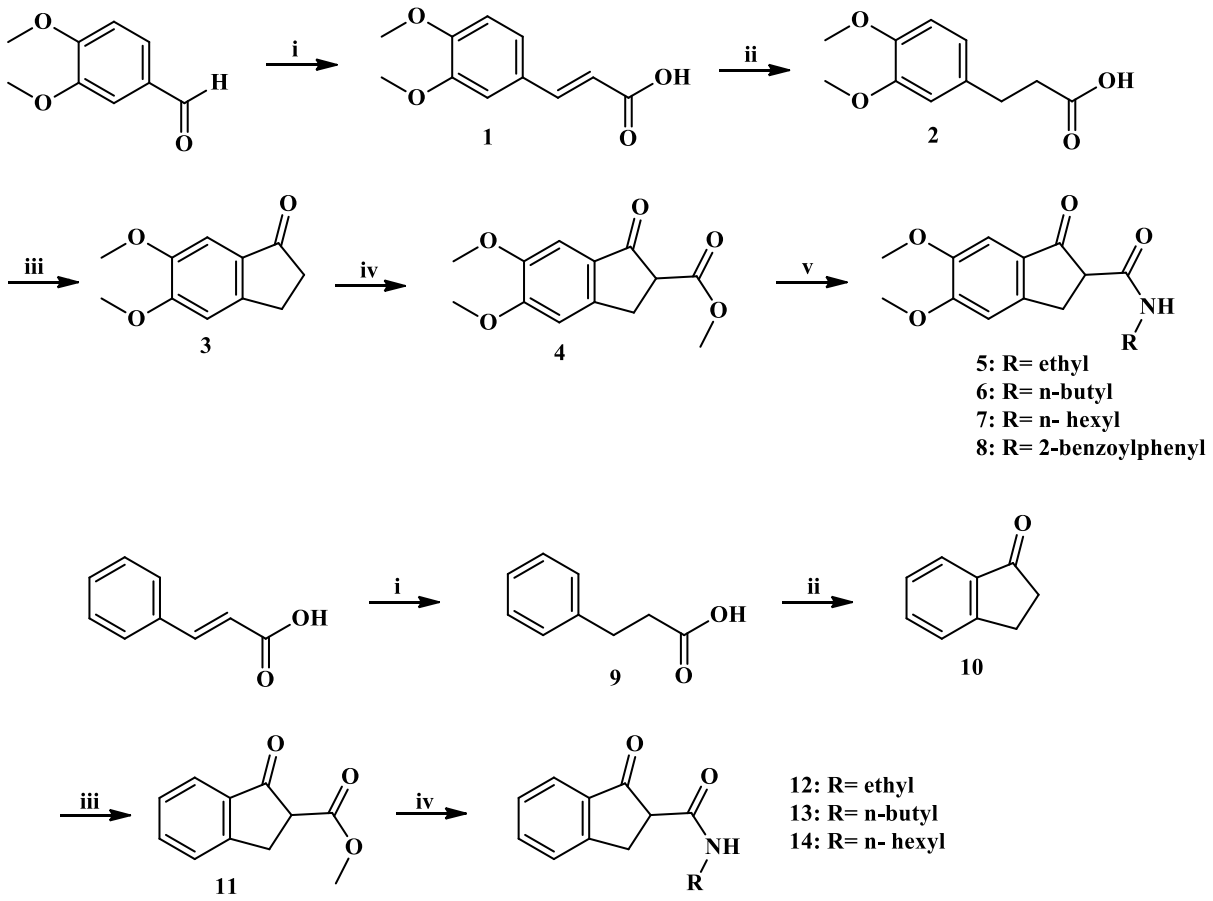
research on enzyme inhibitors, we became interested in isatins and analogs, since for several compounds holding an indene scaffold interesting biological properties have been reported [2, 4-7]. These compounds are also similar to donepezil, and hence it seemed reasonable to investigate their ability to inhibit AChE and/or BChE. As a prerequisite, however, their toxicity/cytotoxicity must be low before they can be used as a drug at a later stage.

2. Results and iscussion

A small library of alkyl indanone-amides was accessed from commercially available 3,4-dimethoxybenzaldehyde and (*E*)-cinnamic acid as depicted in Scheme 1.

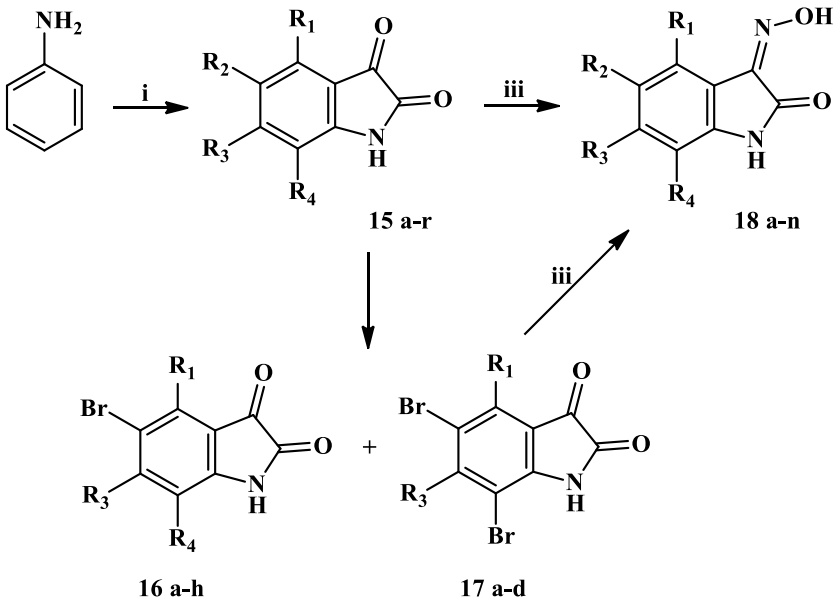


Scheme 1. Synthesis and derivatization of 5,6-dimethoxy-1-indanone: i: malonic acid, piperidine, pyridine, reflux 120°C, 4 h, 80%; ii: Pd/C (10%), H_2, THF, rt, overnight, 82–90%; iii: 1) oxalylchloride, CH_2Cl_2, rt, overnight 2) $AlCl_3$, CH_2Cl_2, 0°C, 24–53%; iv: dimethylcarbonate, NaH, reflux 90°C, 32–78%; v: appropriate amine, 1,4-dioxane, microwave, 8–90%

Thereby, **1** was obtained from a Knoevenagel-condensation in good yields of 80%. Hydrogenation of **1** and (*E*)-cinnamic acid gave compounds **2** and **9** in excellent yields (82% and 90%), respectively. Following the procedure, as described by Koca *et al.*[4] compounds **4** and **11** were used as starting materials for the straightforward synthesis of several amides. We paid particular attention to the synthesis of alkyl amides, as their biological properties are mainly unexplored. Yields in these reactions depended strongly on the length of the alkyl moiety as well as on the substitution pattern of the indanone.

In the second series of compounds, substituted isatins and their oximes were synthesized starting from suitably substituted anilines using Sandmeyer reaction conditions (Scheme 2). Thus, isatins **15a-15r** were obtained in yields ranging between 9 and 94% [8]. Compounds **16a-16h** and **17a-17d** were prepared similarly; the starting materials (brominated at C-5 or C-5 and C-7) were obtained adapting the procedure reported [9] by Tingare *et al.*

The oximes were synthesized following the procedure outlined by Campbell and Warawa [10]. Thus, compounds **18a-18n** could be synthesized in 45–94% isolated yield while their synthesis using other procedures [11-13] resulted in significantly lower yields.



Scheme 2. Synthetic pathway from anilines to oximes via isatin derivatives: i: 1) chloralhydrate, hydroxylamine hydrochloride, Na_2SO_4, rt; 2) H_2SO_4, H_2O, 0°C, 9–94%; ii: Br_2, AcOH (1M), 0°C, 3–96%; iii: hydroxylamine hydrochloride, ethanol, 80°C, 45–94%

Table 1. Substitution patterns for isatins (**15**), 5-Br-isatins (**16**), 5,7-Br-isatins (**17**) and oximes (**18**) as depicted in Scheme 2.

	R^1	R^2	R^3	R^4
a	Cl	H	H	H
b	H	H	Cl	H
c	I	H	H	H
d	H	H	I	H
e	H	H	H	Cl
f	H	H	H	I
g	H	H	F	H
h	H	H	H	F
i	H	H	F	F
j	Me	Me	H	H
k	H	Me	Me	H
l	Br	H	H	H
m	H	H	Br	H
n	H	H	H	Br
o	H	Br	H	H
p	H	I	H	H
q	H	OMe	OMe	H
r	H	NO_2	H	H

All compounds were subjected to a biological evaluation using Ellman's assays employing AChE (from *electrophorus electricus*) and BChE (from *equine serum*); galantamine hydrobromide (GH) was used as a standard. The results from these assays are summarized in Table 1. These assays were performed as previously described [14, 15].

Table 2. Inhibition of AChE (from *electrophorus electricus*) and BChE (from *equine serum*) as determined in Ellman´s assays; inhibition constants K_i and $K_{i'}$ are reported in µM, and **GH** (galantamine hydrobromide) was used as a standard; the results are mean values resulting from triplicate experiments; % inhibition was determined at concentration of 50 µM.

	AChE			**BChE**		
	K_i [µM]	$K_{i'}$ [µM]	type of inhibition	K_i [µM]	$K_{i'}$ [µM]	type of inhibition
	(% inhibition)			(% inhibition)		
GH	0.54 ± 0.01		competitive	9.37 ± 0.67		competitive
1	(43.7)			(12.3)		
2	(7.22)			(1.9)		
3	7.19±0.33	> 100 (37.7)	mixed	(9.2)		
4	18.95±2.19	55.72±3.57	mixed	(13.1)		
5	12.62±1.25	121.64±8.91	mixed	(10.4)		
6	17.01±1.73	> 100 (33.2)	mixed	(12.4)		
7	19.42±2.35		competitive	(11.9)		
8	20.62±0.57	62.23±2.44	mixed	(14.7)		
9	(7.4)			(2.2)		
10	(10.08)			(3.3)		
11	(9.43)			(4.0)		
12	16.70±2.39	> 70	mixed	(1.8)		
13	18.52±1.18	> 70	mixed	(7.5)		
14	12.33±1.32	> 70	mixed	(5.6)		

The results from the Ellman's assays for the isatin derivatives are summarized in Table 3, and only moderate activity was determined for several of the compounds. However, the results for compound **17c** were outstanding, since this compound was shown to be an excellent mixed-type inhibitor for AChE. As far as BChE is concerned, only a small number of substances (**17a**, **17c**, some of **18**) were found to be a good or at least moderate inhibitor for this enzyme. Furthermore, only a few compounds of this series hold the rare property to bind to both enzymes.

Remarkable is the difference between compounds **17a** and **17c** in their ability to inhibit AChE. To get an explanation, we performed additional molecular modelling calculations using AutoDock. These calculations showed for both compounds a high affinity to the enzyme; however, the affinity of **17c** (holding an iodine substituent) to the active site is higher than that of **17a** (with a chlorine substituent); also, the tendency of **17a** to get stuck in its access to the active site seems higher than that of **17c**. The results of these calculations are shown in Fig.2. Binding scores for the different conformations of **17a** and **17c** were calculated, and for **17a** -7.62 to -7.89 kcal/mol and for **17c** -7.38 to -7.40 kcal/mol were found.

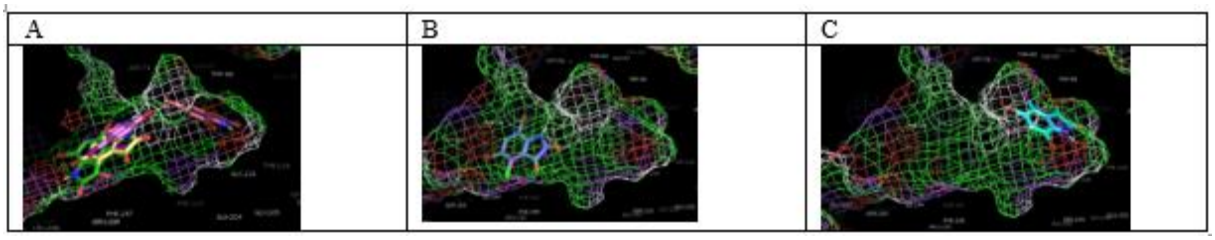


Figure 2. Depiction of the results from the molecular modelling calculations. A: yellow: compound **17a**; brown, green and pink: 3 possible conformations of **17c**; B: location of 18a "being stuck" in the access channel to the active site; C: Location of **17c** in the active site

Table 3. AChE (from *electrophorus electricus*)- and BChE (from *equine serum*)- inhibition determined in Ellman´s assay; K_i and $K_{i'}$ (inhibition constants) in µM for **GH** (galantamine hydrobromide as a standard) and compounds **15-18**; averaged from triplicate experiments; % inhibition were determined at a concentration of 50 µM.

	AChE			**BChE**		
	K_i [µM]	$K_{i'}$ [µM]	type of inhibition	K_i [µM]	$K_{i'}$ [µM]	type of inhibition
GH	0.54 ± 0.01		competitive	9.37 ± 0.67		competitive

15a	13.49±2.27	27.11±8.01	mixed	20.14±1.04		competitive
15b	29.72±8.90	127.01±3.74	mixed	32.76±4.40		competitive
15c	17.72±4.06	145.04±9.13	mixed	> 100		
15d	21.41±1.82		competitive	> 100		
15e	15.29±0.14		competitive	> 100		
15f	13.24±0.78	64.29±3.25	mixed	42.52±2.67	228.85±16.60	mixed
15g	> 100			> 100		
15h	> 100			> 100		
15i	20.04±1.15	111.88±4.46	mixed	> 100		
15j	24.47±5.55	106.71±7.62	mixed	> 100		
15k	18.94±1.59	85.68±3.68	mixed	> 100		
15l	24.12±3.18		competitive	>100		
15m	18.45±2.53	123.80±29.28	mixed	> 100		
15n	17.03±3.28	186.40±18.10	mixed	> 100		
16o	> 100			> 100		
15p	> 100			17.09±3.46		competitive
15q	> 100			> 100		
15r	24.56±5.74	108.67±7.13	mixed	> 100		
16a	(14.9)			(17.7)		
16b	(48.9)			(8.6)		
16c	(17.2)			(23.7)		
16d	13.14±2.31	12.51±0.90	mixed	> 60		
16e	(15.9)			(8.6)		
16f	(34.2)			(17.0)		
16g	(15.2)			(1.4)		
17a	10.54±0.76	34.42±1.25	mixed	5.38±0.88	44.35±7.28	mixed
17c	2.52±0.61	11.74±1.31	mixed	4.49±0.32	6.56±0.57	mixed
	> 100			98.93±19.93	135.37±12.80	mixed
18b	> 100			16.65±1.38		competitive
18c	> 100			65.60±16.80	68.62±11.05	mixed
18d	> 80 (17.6)			14.50±0.48	106.02±6.93	mixed
18e-i	> 100			> 100		
18j	29.70±2.68		competitive	> 100		
18k	> 100			> 100		
18l	> 100			> 100		
18m	> 100			22.58±8.34	76.11±15.55	mixed
19n	> 100			> 100 (16.9)		

Table 4. Cytotoxicity of indanone compounds **1-14**; SRB assay EC_{50} values [µM] after 96 h of treatment; averaged from three independent experiments performed each in triplicate; confidence interval CI = 95%. Human cancer cell lines: FaDu (hypopharyngeal carcinoma), A2780 (ovarian carcinoma), HT29 (colorectal carcinoma), MCF-7 (breast carcinoma), SW1736 (thyroid carcinoma), A375 (malignant melanoma) and non-malignant mouse fibroblasts (NiH 3T3); cut-off 30 µM.

	FaDu	A2780	HT29	MCF-7	SW1736	A375	NIH 3T3
1-11	> 30	> 30	> 30	> 30	> 30	> 30	> 30
12	> 30	> 30	> 30	25.62±3.0	> 30	> 30	> 30
13	> 30	> 30	> 30	23.78±1.6	> 30	> 30	> 30
14	> 30	> 30	> 30	4.28±0.5	> 30	> 30	> 30

In vitro cytotoxicity of the indanones **1-14** and isatin-derivatives **15-18** was screened in colorimetric SRB-assays, and the EC_{50} values were determined using several human tumor cell lines and non-malignant

mouse fibroblasts (NIH 3T3). The results from these assays are compiled in Tables 4 and 5

No cytotoxicity was observed for compounds **1-11** (cut-off: 30 µM), and compounds **12** and **13** showed moderate activity. Compound **14**, however, while being not cytotoxic for several human tumor cell lines, exhibited selective and good cytotoxicity for the human adenocarcinoma breast cell lines MCF-7.

Table 5. Cytotoxicity of isatin compounds **15-18** SRB assay EC_{50} values [µM] after 96 h of treatment; averaged from three independent experiments performed each in triplicate; confidence interval CI = 95%. Human cancer cell lines: FaDu (hypopharyngeal carcinoma), A2780 (ovarian carcinoma), HT29 (colorectal carcinoma), MCF7 (breast carcinoma), SW1736 (thyroid carcinoma), 8505C (thyroid anaplastic carcinoma), and non-malignant mouse fibroblasts (NIH 3T3); cut-off 30 µM.

	FaDu	518A2	A2780	HT29	MCF7	A549	8505C	NiH3T3
15a-c	-	> 30	> 30	> 30	> 30	> 30	> 30	> 30
15d	-	9.2±0.7	10.6±0.3	24.8±1.1	17.4±1.7	> 30	> 30	> 30
15e	-	23.7	> 30	> 30	> 30	> 30	> 30	> 30
15f	-	16.7±0.6	25.5±1.2	> 30	> 30	> 30	> 30	> 30
15g,h	-	> 30	> 30	> 30	> 30	> 30	> 30	> 30
15i	-	14.9±0.4	12.1±0.7	23.8±1.7	21.5±3.0	18.2±1.1	27.4±0.4	15.2±1.6
15j-l	-	> 30	> 30	> 30	> 30	> 30	> 30	> 30
15m	-	8.6±0.8	9.1±0.4	22.6±2.5	19.7±2.1	> 30	> 30	> 30
15n	-	27.3±0.6	> 30	> 30	> 30	> 30	> 30	> 30
15o	-	9.8±0.6	> 30	> 30	> 30	24.4±1.6	12.0±0.9	> 30
15p	-	6.5±0.6	7.3±0.6	30.3±2.4	25.5±2.9	> 30	> 30	28.7±3.0
15q,r	> 30	> 30	> 30	> 30	> 30	> 30	> 30	> 30
16a	> 30	17.2±0.2	> 30	> 30	25.7±0.2	13.9±1.3	16.6±0.1	19.9±0.9
16b	10.9±2.1	-	7.7±1.8	-	13.7±0.9	-	-	-
16c	14.6±1.4	-	9.9±0.6	-	16.1±0.8	-	-	-
16d	19.6±2.8	-	13.3±2.1	-	20.5±1.1	-	-	-
16e	-	10.6±1.9	> 30	> 30	> 30	> 30	17.7±0.6	> 30
16f	-	9.0±0.6	> 30	> 30	> 30	22.0±0.8	12.8±0.2	> 30
16g	8.95±0.7	-	6.47±0.8	-	12.29±1.0	-	-	-

	FaDu	**518A2**	**A2780**	**HT29**	**MCF7**	**A549**	**NiH3T3**
17a-d	> 30	> 30	> 30	> 30	> 30	> 30	> 30
18a-n	> 30	> 30	> 30	> 30	> 30	> 30	> 30

For several of the isatins **15-18** only low or no cytotoxicity was found. This is a prerequisite for the possible use of these compounds as inhibitors of cholinesterases in ongoing investigations presently studied in more detail in our laboratories.

3. Conclusion

A small library consisting of 49 indanone-amides and substituted isatin derivatives has been investigated for the ability of these compounds to act as inhibitors for the enzymes acetyl- and butyrylcholinesterase (AChE, BChE). Among these compounds, 5,7-dibromo-4-iodoisatin (**17c**) was shown to be a good mixed-type inhibitor for AChE (K_i = 2.52 ± 0.61 µM and $K_{i'}$ = 11.74 ± 1.31 µM) but this compound also acted as a dual inhibitor for BChE (K_i = 4.49 ± 0.32 µM and $K_{i'}$ = 6.56 ± 0.57 µM). Interestingly, *N*-hexyl-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**14**) was cytotoxic especially for MCF-7 breast adenocarcinoma cells (EC_{50} = 4.28 µM).

4. Experimental

NMR spectra were recorded using the Varian spectrometers Gemini 2000 or Unity 500 (δ given in ppm, *J* in Hz; typical experiments: H-H-COSY, HMBC, HSQC, NOESY), MS spectra were taken on a Finnigan MAT LCQ 7000 (electrospray, voltage 4.1 kV, sheath gas nitrogen) instrument. TLC was performed on silica gel (Merck 5554, detection with cerium molybdate reagent); melting points are uncorrected (*Leica* hot stage microscope or BÜCHI Melting Point M-565), and elemental analyses were performed on a Foss-Heraeus Vario EL (CHNS) unit. IR spectra were recorded on a Perkin Elmer FT-IR spectrometer Spectrum 1000 or on a Perkin-Elmer Spectrum Two (UATR Two Unit). The solvents were dried according to usual procedures. The purity of the compounds was determined by HPLC and found to be >96%.

(2*E*)-3-(3,4-Dimethoxyphenyl)-2-propenoic acid (1)

To a solution of 3,4-dimethoxybenzaldehyde (8.30 g, 50 mmol) and malonic acid (6.25 g, 60 mmol) in pyridine (125 mL) at 120°C piperidine (0.2 mL, 2 mmol) was added, and the reaction mixture was heated under reflux for 4 h. Usual aqueous work-up followed by re-crystallization from EtOH gave **1** [16] (8.28 g, 80%) as an off-white solid;
R_F = 0.05 (silica gel, *n*-hexane/ethyl acetate, 4:1);
mp = 178–180°C (lit.: [17] 181-183°C);
MS (ESI, MeOH): m/z (%) = 207.0 ([M-H]$^-$, 11), 415.1 ([2M-H]$^-$, 100), 436.9 ([2M-2H+Na]$^-$, 13).

3-(3,4-Dimethoxyphenyl)propanoic acid (2)

A solution of **1** (1 g, 4.8 mmol) in dry THF (20 mL) was hydrogenated overnight at 75 psi in the presence of Pd/C (10%, 0.116 g). Usual work-up gave **2** (0.83 g, 82%) [18] as a white solid;
R_F = 0.09 (silica gel, *n*-hexane/ethyl acetate, 4:1);
mp = 98–99°C (lit.: [19] 98-99°C);
MS (ESI, MeOH): m/z (%) = 209.1 ([M-H]$^-$, 100), 441 ([2M-2H+Na]$^-$, 71).

5,6-Dimethoxy-indane-1-one (3)

To an ice-cold solution of **2** (0.5 g, 2.37 mmol) in dry dichloromethane (8 mL), oxalyl chloride (0.803 mL, 9.5 mmol) and dimethylformamide (5 drops) were added. After an additional stirring at room temperature for 1 h, the solvents were evaporated. The residue was dissolved in dry dichloromethane (8 mL), and at 0°C $AlCl_3$ (0.57 g, 4.3 mmol) was added in several portions. After stirring at room temperature for 1 h at room temperature followed by usual work-up and re-crystallization from EtOH, **3** (0.11 g, 24%) [4] was obtained as an off-white solid;
R_F = 0.39 (silica gel, *n*-hexane/ethyl acetate, 1:1);
mp = 117–118°C (lit.: [20] 117-119°C);
MS (ESI, MeOH): m/z (%) = 193.2 ([M+H]$^+$, 100), 215.0 ([M+Na]$^+$, 34).

5,6-Dimethoxy-1-oxo-indan-2-carboxylic acid methyl ester (4)

To a solution of **3** (4.00 g, 20 mmol) in dimethylcarbonate (22 mL), NaH (2.4 g, 60 mmol, 60% in mineral oil) was added, and the mixture was stirred at 90°C for 2 h. Usual aqueous work-up followed by re-crystallization from EtOH gave **4** (3.92 g, 78%) [4] as lightly yellowish needles;
R_F = 0.12 (silica gel, chloroform); mp = 160–163°C (lit.: [21] 161–162°C);
MS (ESI, MeOH): m/z (%) = 251.1 ([M+H]$^+$, 100), 273.1 ([M+Na]$^+$, 43), 277.7 ([2M+Na+MeOH]$^+$,10), 285.7 ([2M+K+H+MeOH]$^{2+}$, 11).

General Procedure A

To a solution of compound **4** (1.2 mmol) was dissolved in dry 1,4-dioxane (3 mL), the corresponding amine (1.2 mmol) was added, and the solution was sonicated in an ultrasound bath for 1 min followed by microwave irradiation for 10 min (1200 rpm, 300 W, 170°C) [4]. The solvent was removed under reduced pressure, and the residue was subjected to recrystallization from EtOH.

Compounds **5–8** and **12–15** were prepared following procedure A.

***N*-Ethyl-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (5)**

Compound **5** (0.22 g, 70%) was obtained as a white solid;
R_F = 0.21 (silica gel, *n*-hexane/ethyl acetate, 1:1);
mp = 188–192°C,
IR (KBr): ν = 3284*m*, 3083*w*, 2938*w*, 1702*s*, 1634*s*, 1592*m*, 1554*m*, 1503*s*, 1458*m*, 1363*w*, 1311*s*, 1267*s*, 1222*m*, 1200*w*, 1151*w*, 1115*m*, 1032*m* cm^{-1};
UV-vis ($CHCl_3$): λ (log ε) = 251 (3.57), 295 (3.96), 348 (4.06) nm;
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (*s*, 1H, 7-H), 6.90 (*s*, 1H, 4-H), 3.96 (*s*, 3H, 9-H), 3.88 (*s*, 3H, 10-H), 3.64 (*dd*, *J* = 3.6, 0.9 Hz, 1H, 3_a-H), 3.50 (*dd*, *J* = 7.9, 3.6 Hz, 1H, 2-H), 3.37–3.27 (*m*, 2H, 1´-H), 3.23 (*dd*, *J* = 17.5, 7.9 Hz, 1H, 3_b-H), 1.16 (*t*, *J* = 7.3 Hz, 3H, 2´-H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$): δ = 202.0 (C-1), 166.8 (C-8), 156.6 (C-5), 150.3 (C-7a), 149.8 (C-6), 128.1 (C-3a), 107.6 (C-4), 104.6 (C-7), 56.5 (C-9), 56.2 (C-10), 53.2 (C-2), 34.8 (C-1´), 28.6 (C-3), 14.9 (C-2´) ppm;
MS (ESI, MeOH): m/z (%) = 264.1 ([M+H]$^+$, 46), 286.1 ([M+Na]$^+$, 38), 298.7 ([2M+Ca+MeOH]$^{2+}$, 16), 414.6 ([3M+Ca]$^{2+}$, 30), 548.8 ([2M+Na]$^+$, 100);
analysis calcd for $C_{14}H_{17}NO_4$ (263.29): C 63.87, H 6.51, N 5.32; found C 63.66, H 6.79, N 5.11.

***N*-Butyl-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (6)**

Compound **6** (0.32 g, 90%) was obtained as a white solid;
R_F = 0.57 (silica gel, *n*-hexane/ethyl acetate, 1:1);
mp = 152–154°C; IR (KBr): ν = 3445*m*, 3291*s*, 2925*m*, 2870*w*, 1704*s*, 1638*s*, 1592*m*, 1554*m*, 1505*s*, 1443*m*, 1367*w*, 1313*s*, 1268*s*, 1224*m*, 1200*w*, 1116*m*, 1030*m* cm^{-1};
UV-vis ($CHCl_3$): λ (log ε) = 251 (3.59), 295 (3.97), 347 (4.03) nm;
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (*s*, 1H, 7-H), 6.92 (*s*, 1H, 4-H), 3.98 (*s*, 3H, 9-H), 3.91 (*s*, 3H, 10-H), 3.70 (*dd*, *J* = 17.6, 3.5 Hz, 1H, 3_a-H), 3.52 (*dd*, *J* = 7.9, 3.6 Hz, 1H, 2-H), 3.31 (*ddd*, *J* = 12.8, 7.3, 2.1 Hz, 2H, 1´-H), 3.28–3.22 (*m*, 1H, 3_b-H), 1.58–1.50 (m, 2H, 2´-H), 1.44–1.31 (*m*, 2H, 3´-H), 0.93 (*t*, *J* = 7.3 Hz, 3H, 4´-H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$): δ = 199.4 (C-1), 166.3 (C-8), 157.6 (C-5), 150.2 (C-7a), 149.5 (C-6), 128.0 (C-3a), 107.6 (C-4), 104.7 (C-7), 56.5 (C-9), 56.2 (C-10), 53.2 (C-2), 39.7 (C-1´), 31.7 (C-2´), 28.7 (C-3), 20.3 (C-3´), 14.1 (C-4´) ppm;
MS (ESI, MeOH): m/z (%) = 292.1 ([M+H]$^+$, 41), 314.2 ([M+Na]$^+$, 27), 318.7 ([2M+Na+H+MeOH]$^{2+}$, 3), 326.7 ([2M+Ca+MeOH]$^{2+}$, 13), 448.6 ([3M+Na+H]$^{2+}$, 6), 456.6 ([3M+Ca]$^{2+}$, 29), 604.9 ([2M+Na]$^+$), 100);
analysis calcd for $C_{16}H_{21}NO_4$ (291.35): C 65.96, H 7.27, N 4.81; found C 65.77, H 7.45, N 4.51.

***N*-Hexyl-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (7)**

Compound **7** (0.04 g, 11%) was obtained as a white solid;

R_F = 0.53 (silica gel, *n*-hexane/ethyl acetate, 1:1);
mp = 136–139°C;
IR (KBr): ν = 3752*w*, 3441*m*, 3289*m*, 2930*m*, 1702*m*, 1636*s*, 1592*m*, 1504*s*, 1458*m*, 1312*s*, 1268*s*, 1223*m*, 1115*m*, 1031*m* cm^{-1}; UV-vis ($CHCl_3$): λ (log ε) = 251 (3.60), 294 (3.96), 346 (4.02) nm;
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (*s*, 1H, 7-H), 6.91 (*s*, 1H, 4-H), 3.98 (*s*, 3H, 9-H), 3.90 (*s*, 3H, 10-H), 3.70 (*dd*, *J* = 17.4, 3.5 Hz, 1H, 3_a-H), 3.52 (*dd*, *J* = 7.9, 3.6 Hz, 1H, 2-H), 3.35 – 3.23 (*m*, 2H, 1´-H), 3.25 (*dd*, *J* = 17.4 Hz, 7.7 Hz, 1H, 3_b-H), 1.54 (*p*, *J* = 7.1 Hz, 2H, 2´-H), 1.37–1.31 (*m*, 2H, 3´-H), 1.31 – 1.27 (m, 4H, 4´-H + 5´-H), 0.90–0.86 (*m*, 3H, 6´-H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$): δ = 202.1 (C-1), 166.8 (C-8), 156.6 (C-5), 150.3 (C-7a), 149.8 (C-6), 128.2 (C-3a), 107.6 (C-4), 104.6 (C-7), 56.5 (C-9), 56.3 (C-10), 53.2 (C-2), 40.0 (C-1´), 31.6 (C-4´), 29.6 (C-2´), 28.7 (C-3), 26.7 (C-3´), 22.7 (C-5´), 14.2 (C-6´) ppm;
MS (ESI, MeOH): m/z (%) = 320.2 ($[M+H]^+$, 32), 342.2 ($[M+Na]^+$, 16), 354.8 ($[2M+K+H+MeOH]^{2+}$, 5), 498.7 ($[3M+Ca]^{2+}$, 13), 660.9 ($[2M+Na]^+$, 100);
analysis calcd for $C_{18}H_{25}NO_4$ (319.40): C 67.69, H 7.89, N 4.39; found C 67.50, H 8.02, N 4.11.

***N*-(2-Benzoylphenyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (8)**
Compound **8** (0.12 g, 70%) was obtained as a white solid;
R_F = 0.5 (silica gel, *n*-hexane/ethyl acetate, 1:1);
mp = 190–192°C;
IR (KBr): ν = 3517*m*, 3228*m*, 2923*w*, 2850*w*, 1686*s*, 1590*m*, 1502*m*, 1450*w*, 1371*w*, 1315*s*, 1276*m*, 1224*w*, 1191*w*, 1114*m*, 1055*w*, 1033*w*, 754*m* cm^{-1};
UV-vis ($CHCl_3$): λ (log ε) = 298 (4.06), 354 (4.03) nm;
^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.55 (*s*, 1H, NH), 7.42 (*ddd*, *J* = 8.2, 2.6, 1.2 Hz, 3H, 2´´-H + 3_a´´-H), 7.32 (*dd*, *J* = 8.5, 6.9 Hz, 2H, 3_b´´-H + 3´-H), 7.25–7.20 (*m*, 1H, 4´´-H), 7.16 (*dd*, *J* = 15.3, 1.5 Hz, 1H, 5´-H), 7.15 (*s*, 1H, 7-H), 6.96 (*td*, *J* = 7.5, 1.1 Hz, 1H, 4´-H), 6.93 (*s*, 1H, 4-H), 6.92–6.89 (*m*, 1H, 6´-H), 3.87 (*s*, 3H, 9-H), 3.77 (*s*, 3H, 10-H), 3.58 (*s*, 1H, 2-H), 3.52 (*d*, *J* = 17.0 Hz, 1H, 3_a-H), 3.04 (*d*, *J* = 17.0 Hz, 1H, 3_b-H) ppm; ^{13}C NMR (100 MHz; DMSO-d_6): δ = 197.4 (C-7´ + C-1), 167.9 (C-8), 155.5 (C-5), 150.0 (C-7a), 149.1 (C-6), 146.1 (C-3a), 135.8 (C-1´), 130.4 (C-2´), 128.2 (C-3´), 127.8 (C-5´), 127.1 (C-1´´), 127.0 (C-4´´), 125.3 (C-2´´), 124.8 (C-3´´), 122.4 (C-4´), 114.5 (C-6´), 107.8 (C-7), 104.2 (C-4), 66.0 (C-2), 56.0 (C-9), 55.6 (C-10), 32.7 (C-3) ppm;
MS (ESI, MeOH): m/z (%) = 398.2 ($[M+H-H_2O]^+$, 24), 438.0 ($[M+Na]^+$, 38), 642.5 ($[3M+Ca]^{2+}$, 10), 852.9 ($[2M+Na]^+$, 100);
analysis calcd for $C_{25}H_{21}NO_5$ (415.44): C 72.28, H 5.10, N 3.37; found C 71.98, H 5.34, N 3.11.

3-Phenylpropanoic acid (9)
Hydrogenation of cinnamic acid (1 g, 6.75 mmol) with Pd/C (10%, 0.134 g) in THF (20 mL). for 6 h at 75 psi followed by usual work-up gave **9** (0.91 g, 90%) [15] as a white solid; R_F = 0.45 (silica gel, *n*-hexane/ethyl acetate, 4:1); mp = 45–48°C (lit.: [22] 48-50°C); MS (ESI, MeOH): m/z (%) = 149.1 ($[M-H]^-$, 82), 321.0 ($[2M-2H+Na]^-$, 100).

2,3-Dihydro-1H-inden-1-one (10)
Reaction of **9** (0.5 g, 3.3 mmol) in dry dichloromethane (8 mL) at 0°C with oxalyl chloride (1.12 mL, 13.2 mmol) and DMF (5 drops) followed by an additional reaction for 1 h at room temperature, usual work-up and reaction with $AlCl_3$ (0.80 g, 5.98 mmol) in dry dichloromethane (8 mL) as described above and re-crystallization from EtOH gave **3** (0.23 g, 53%) as an off-white solid; R_F = 0.48 (silica gel, *n*-hexane/ethyl acetate, 4:2); mp = 39–40°C (lit.: [23] 38–39°C); MS (ESI, MeOH): m/z (%) = 133.1 ($[M+H]^+$, 100), 155.0 ($[M+Na]^+$, 16).

Methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (11)
As described for the synthesis of **4**, from **10** (3.00 g, 22.7 mmol) and NaH (2.73 g, 68.1 mmol, 60% in mineral oil)
followed by re-crystallization from EtOH, **11** (1.38 g, 32%) was obtained as an off-white solid;
R_F = 0.13 (silica gel, chloroform); mp = 49–51°C;
IR (ATR): ν = 1705*s*, 1586*m*, 1464*m*, 1438*m*, 1317*m*, 1273*m*, 1208*s*, 1157*s*, 1095*m*, 1007*m*, 987*s*, 951*m*, 853*m*, 767*s*, 735*m*, 675*m*, 513*m*, 466*m* cm^{-1}; UV-vis (MeOH): λ (log ε) = 205 (4.07), 246 (3.73), 296 (3.43) nm;
^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (*d*, *J* = 7.7 Hz, 1H, 7-H), 7.66–7.61 (*m*, 1H, 6-H), 7.51 (*dd*, *J* = 7.7, 0.9 Hz, 1H, 4-H), 7.43–7.38 (*m*, 1H, 5-H), 3.80 (*s*, 3H, 1´-H), 3.74 (*dd*, *J* = 17.2, 4.0 Hz, 1H, 2-H), 3.57 (*dd*, *J* = 17.2, 4.0 Hz, 1H, 3_a-H), 3.38 (*dd*, *J* =17.3, 8.3 Hz, 1H, 3_b-H) ppm ; ^{13}C NMR (100 MHz; $CDCl_3$): δ = 178.8 (C-1), 170.0 (C-8), 153.7 (C-3a), 135.6 (C-6), 135.4 (C-7a), 128.0 (C-5), 126.7 (C-4), 124.9 (C-7), 53.3 (C-2), 52.9 (C-1´), 30.4 (C-3) ppm;
MS (ESI, MeOH): m/z (%) = 191.0 ($[M+H]^+$, 100), 207.9 ($[M+NH_4]^+$, 21), 213.1 ($[M+Na]^+$, 79), 225.8 ($[2M+Ca+MeOH]^{2+}$, 23);
analysis calcd for $C_{11}H_{10}O_3$ (190.20): C 69.46, H 5.30; found C 69.25, H 5.47.

***N*-Ethyl-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (12)**
Following the general procedure A, compound **12** (0.04 g, 15%) was obtained as an off-white solid;
R_F = 0.08 (silica gel, *n*-hexane/ethyl acetate, 4:1);
mp = 141–144°C; IR (ATR): ν = 3300*m*, 1721*s*, 1632*s*, 1552*s*, 1462*m*, 1421*m*, 11361*m*, 1324*m*, 1269*s*, 1246*m*, 1212*s*, 1150*m*, 1011*m*, 993*m*, 764*s*, 668*s*, 592*m*, 497*m*, 465*s* cm^{-1};
UV-vis (MeOH): λ (log ε) = 204 (4.35), 246 (3.95), 295 (3.39) nm;
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (*d*, *J* = 7.7 Hz, 1H, 7-H), 7.63 (*t*, *J* = 7.4 Hz, 1H, 6-H), 7.52 (*d*, J = 7.7 Hz, 1H, 4-H), 7.38 (*t*, *J* = 7.4 Hz, 1H, 5-H), 3.80 (*dd*, *J* = 17.7, 3.9 Hz, 1H, 3_a-H), 3.54 (*dd*, *J* = 8.3, 4.0 Hz, 1H, 2-H), 3.40–3.35 (*m*, 1H, 3_b-H), 3.35–3.30 (*m*, 2H,1´-H), 1.19 (*t*, *J* = 7.3 Hz, 3H, 2´-H) ppm; ^{13}C NMR (125 MHz; $CDCl_3$): δ = 203.8 (C-1), 166.3 (C-

8), 154.5 (C-3a), 135.9 (C-6), 135.6 (C-7a), 127.7 (C-5), 126.9 (C-4), 124.5 (C-7), 52.99 (C-2), 34.9 (C-1´), 28.9 (C-3), 14.9 (C-2´) ppm;
MS (ESI, MeOH): m/z (%) = 204.1 ([M+H]$^+$, 100), 226.1 ([M+Na]$^+$, 81), 230.8 ([2M+Na+H+MeOH]$^{2+}$, 16), 238.8 ([2M+Ca+MeOH]$^{2+}$, 27);
analysis calcd for $C_{12}H_{13}NO_2$ (203.24): C 70.92, H 6.45, N 6.89; found C 70.77, H 6.61, N 6.60.

_N_-Butyl-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (13)

Following the general procedure A, compound **13** (0.04 g, 13%) was obtained as a white solid; R_F = 0.08 (silica gel, *n*-hexane/ethyl acetate, 4:1);
mp = 112–113°C;
IR (ATR): ν = 3311*w*, 2929*w*, 1715*s*, 1634*s*, 1538*s*, 1463*m*, 1423*w*, 1357*m*, 1326*m*, 1273*m*, 1211*m*, 1150*w*, 1061*m*, 773*m*, 671*s*, 594*m*, 467*m* cm^{-1}; UV-vis (MeOH): λ (log ε) = 204 (4.18), 246 (3.77), 296 (3.20) nm;
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (*d*, *J* = 7.7 Hz, 1H, 7-H), 7.63 (*td*, *J* = 7.5, 1.2 Hz, 1H, 6-H), 7.53–7.51 (*m*, 1H, 4-H), 7.40–7.37 (*m*, 1H, 5-H), 3.80 (*dd*, *J* = 17.8, 4.1 Hz, 1H, 3_a-H), 3.54 (*dd*, *J* = 8.3, 4.0 Hz, 1H, 2-H), 3.39–3.34 (*m*, 1H, 3_b-H), 3.34–3.29 (*m*, 2H, 1´-H), 1.57–1.51 (m, 2H, 2´-H), 1.42 – 1.34 (*m*, 2H, 3´-H), 0.94 (*t*, *J* = 7.3 Hz, 3H, 4´-H) ppm;
^{13}C NMR (125 MHz; $CDCl_3$): δ = 201.0 (C-1), 166.4 (C-8), 154.5 (C-3a), 135.9 (C-6), 135.6 (C-7a), 127.7 (C-5), 126.9 (C-4), 124.5 (C-7), 53.0 (C-2), 39.7 (C-1´), 31.7 (C-2´), 28.9 (C-3), 20.3 (C-3´), 13.9 (C-4´) ppm;
MS (ESI, MeOH): m/z (%) = 232.1 ([M+H]$^+$, 100), 254.1 ([M+Na]$^+$, 77), 258.8 ([2M+Na+H+MeOH]$^{2+}$, 16), 266.8 ([2M+Ca+MeOH]$^{2+}$, 38);
analysis calcd for $C_{14}H_{17}NO_2$ (231.39): C 72.70, H 7.41, N 6.06; found C 72.51, H 7.96, N 5.81.

_N_-Hexyl-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (14)

Following the general procedure A, compound **14** (0.03 g, 8%) was obtained as a white solid; R_F = 0.13 (silica gel, *n*-hexane/ethyl acetate, 4:1);
mp = 103–105°C;
IR (ATR): ν = 3318*w*, 2926*w*, 1714*s*, 1633*s*, 1532*s*, 1462*m*, 1422*w*, 1326*m*, 1273*s*, 1211*m*, 1011*m*, 773*m*, 670*s*, 592*m*, 467*m* cm^{-1}; UV-vis (MeOH): λ (log ε) = 204 (4.41), 246 (3.99), 295 (3.46), 342 (3.24) nm;
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (*d*, *J* = 7.7 Hz, 1H, 7-H), 7.63 (*dt*, *J* = 7.6, 1.1 Hz, 1H, 6-H), 7.52 (*dt*, *J* = 7.7, 0.9 Hz, 1H, 4-H), 7.40–7.36 (*m*, 1H, 5-H), 3.80 (*dd*, *J* = 17.8, 4.0 Hz, 1H, 3_a-H), 3.54 (*dd*, *J* = 8.4, 4.0 Hz, 1H, 2-H), 3.39–3.34 (*m*, 1H, 3_b-H), 3.34–3.27 (*m*, 2H, 1´-H), 1.58–1.52 (*m*, 2H, 2´-H), 1.39–1.28 (*m*, 6H, 3´-H + 4´-H + 5´-H), 0.92–0.85 (*m*, 3H, 6´-H) ppm; ^{13}C NMR (125 MHz; $CDCl_3$): δ = 202.6 (C-1), 166.4 (C-8), 154.5 (C-3a), 135.9 (C-6), 135.6 (C-7a), 127.7 (C-5), 126.9 (C-4), 124.5 (C-7), 53.0 (C-2), 40.1 (C-1´), 31.6 (C-2´), 29.6 (C-3), 28.9 (C-3´), 26.7 (C-4´), 22.7 (C-5´), 14.2 (C-6´) ppm;
MS (ESI, MeOH): m/z (%) = 260.1 ([M+H]$^+$, 100), 282.2 ([M+Na]$^+$, 77), 286.9 ([2M+Na+H+MeOH]$^{2+}$, 19), 294.8 ([2M+Ca+MeOH]$^{2+}$, 32);
analysis calcd for $C_{16}H_{21}NO_2$ (259.35): C 74.10, H 8.16, N 5.40; found C 73.87, H 8.23, N 5.18.

General procedure B

Chloral hydrate (1.1 eq.) was solved in water (2.5 mL/mmol) and heated to 35°C. Sodium sulfate (8.9 eq.) was added by portions and stirred until the solution became clear. The corresponding aniline (1 eq.) was suspended in water (0.7 mL/mmol) and added to this solution. Hydrochloric acid (36%, 3.5 eq.) was added dropwise and a white precipitate was formed. A solution of hydroxyl ammonium chloride (3.2 eq.) in water (1 mL/mmol) was added; this mixture was heated to 80°C until the reaction was completed (as indicated by TLC) [5]. The precipitate was filtrated off at 50°C, washed with water and dried in vacuum. Sulfuric acid (98%, 74 eq.) was heated to 50°C, and the solid was added in several portions. After completion of the reaction, the mixture was poured onto ice (ca. 600 mL). The precipitate was filtrated off and washed with water. To separate the 4- and 6-isomers, the solid was solved in sodium hydroxide solution (10%) at 60°C and neutralized with acetic acid until pH = 5. The 4-isomer was crystallized at 5°C and was filtered off and washed with water. The 6-isomer crystallized after adjusting the pH = 1 by adding concentrated HCl and standing at 5°C.

Compounds **15a-r** were prepared according to general procedure B.

4-Chloroisatin (15a)

Compound **15a** (2.00 g, 36%) was obtained as an orange solid; R_F = 0.17 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 250–255°C (lit.: [24] 251°C);
MS (ESI-MeOH): m/z (%) = 180.8 ([M+H]$^+$, 6), 199.0 ([M+NH_4]$^+$, 29), 204.1 ([M-Na]$^+$, 100), 230.9 ([M+NH_4+MeOH]$^+$, 38), 236.0 ([M+Na+MeOH]$^+$, 62), 384.8 ([2M+Na]$^+$, 28), 416.7 ([2M+Na+MeOH]$^+$, 14), 448.9 ([2M+Na+2MeOH]$^+$, 6), 180.0 ([M-H]$^-$, 100), 211.9 ([M-H+MeOH]$^-$, 11), 215.9 ([M+^{35}Cl]$^-$, 29), 360.7 ([2M-H]$^-$, 8), 392.8 ([2M-H+MeOH]$^-$, 10).

6-Chloroisatin (15b)

Compound **15b** (1.40 g, 25%) was obtained as an orange solid; R_F = 0.27 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 260–263°C (lit.: [25] 261–262°C);
MS (ESI, MeOH): m/z (%) = 198.9 ([M+NH_4]$^+$, 42), 204.0 ([M+Na]$^+$, 100), 230.9 ([M+NH_4+MeOH]$^+$, 69), 236.0 ([M+Na+MeOH]$^+$, 64), 384.9 ([2M+Na]$^+$, 62), 416.7 ([2M+Na+MeOH]$^+$, 51), 180.0 ([M-H]$^-$, 100), 211.9 ([M-H+MeOH]$^-$, 6)

4-Iodoisatin (15c)

Compound **15c** (6.06 g, 72%) was obtained as a reddish-brown solid; R_F = 0.20 (toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 236–240°C;
IR (KBr): *ν* = 3564*m*, 3492*m*, 3454*m*, 3274*s*, 3078*m*, 3040*m*, 2976*m*, 2910*w*, 2858*w*, 2820*w*, 2768*w*, 2696*w*, 2622*w*, 1742*vs*, 1724*vs*, 1634*m*, 1606*vs*,

1578*vs*, 1472*m*, 1436*s*, 1316*m*, 1274*m*, 1242*s*, 1194*w*, 1158*s*, 1136*m*, 1054*w*, 1022*w*, 900*m*, 792*m*, 664*m*, 646*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 229 (4.25), 326 (3.55) nm; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.06 (*s*, 1H, NH), 7.48 (*dd*, *J* = 7.9, 0.7 Hz, 1H, 5-H), 7.25 (*t*, *J* = 7.9 Hz, 1H, 6-H), 6.90 (*dd*, *J* = 7.8, 0.7 Hz, 1H, 7-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 183.6 (C-3), 159.3 (C-2), 154.1 (C-8), 138.4 (C-6), 132.8 (C-5), 119.3 (C-3a), 112.0 (C-7), 92.9 (C-4) ppm;
MS (ESI, MeOH): m/z (%) = 274.0 ($[M+H]^+$, 5), 290.8 ($[M+NH_4]^+$, 37), 296.0 ($[M+Na]^+$, 100), 306.0 ($[M+H+MeOH]^+$, 15), 323.0 ($[M+NH_4+MeOH]^+$, 41), 327.5 ($[M+Na+MeOH]^+$, 59), 568.6 ($[2M+Na]^+$, 80), 600.6 ($[2M+Na+MeOH]^+$, 22), 632.7 ($[2M+Na+2MeOH]^+$, 9), 272.0 ($[M-H]^-$, 100), 303.8 ($[M-H+MeOH]^-$, 19), 307.8 ($[M+Cl]^-$, 52), 544.5 ($[2M-H]^-$, 35);
analysis calcd for $C_8H_4INO_2$ (273.03): C 35.19, H 1.48, N 5.13; found C 34.77, H 1.72, N 4.90.

6-Iodoisatin (15d)
Compound **15d** (0.75 g, 9%) was obtained as an orange solid; R_F = 0.33 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 267–272°C;
IR (KBr): *v* = 3508*m*, 3462*m*, 3190*m*, 3166*m*, 3094*w*, 3064*w*, 3022*w*, 2850*w*, 2802*w*, 2362*w*, 2342*w*, 1744*s*, 1730*vs*, 1610*vs*, 1542*w*, 1508*w*, 1474*w*, 1458*w*, 1434*m*, 1384*w*, 1368*w*, 1326*m*, 1270*w*, 1250*w*, 1196*m*, 1186*w*, 1130*w*, 1102*m*, 1048*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 217 (4.07), 236 (4.07), 259 (4.07), 316 (4.07), 402 (3.37) nm; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.19 (*s*, 1H, NH), 7.47 (*d*, *J* = 6.3 Hz, 1H, 4-H), 7.30 (*s*, 1H, 7-H), 7.24 (*dd*, *J* = 7.5, 1.0 Hz, 1H, 5-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 183.6 (C-3), 159.0 (C-2), 151.1 (C-7a), 131.5 (C-5), 125.6 (C-4), 120.6 (C-7), 117.2 (C-3a), 107.1 (C-6) ppm;
MS (ESI, MeOH): m/z (%) = 272.0 ($[M-H]^-$, 100), 289.9 ($[M-H+H_2O]^-$, 4), 303.8 ($[M-H+MeOH]^-$, 6), 307.7 ($[M+^{35}Cl]^-$, 2);
analysis calcd for $C_8H_4INO_2$ (273.03): C 35.19, H 1.48, N 5.13; found C 34.96, H 1.69, N 4.93

7-Chloroisatin (15e)
Compound **15e** (0.52 g, 94%) was obtained as a reddish-brown solid; R_F = 0.37 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 182–185°C (lit.: [26] 184–186°C);
MS (ESI, MeOH): m/z (%) = 199.0 ($[M+NH_4]^+$, 17), 204.0 ($[M+Na]^+$, 93), 230.9 ($[^{35}M+NH_4+MeOH]^+$, 40), 236.0 ($[M+Na+MeOH]^+$, 100), 180.0 ($[^{35}M-H]^-$, 100).

7-Iodoisatin (15f)
Compound **15f** (2.97 g, 71%) was afforded as a brownish solid; R_F = 0.43 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 267–272°C;
IR (KBr): *v* = 3446*w*, 3208*m*, 3178*m*, 3098*w*, 3064*w*, 2852*w*, 2772*w*, 2594*w*, 1740*vs*, 1646*w*, 1604*vs*, 1540*w*, 1472*m*, 1426*m*, 1382*w*, 1320*s*, 1280*w*, 1262*w*, 1218*m*, 1198*m*, 1174*m*, 1116*m*, 1082*w*, 1052*w*, 956*m*, 764*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 225 nm (4.15), 305 nm (3.45), 405 nm (3.45);
^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.00 (*s*, 1H, NH), 7.94 (*dd*, *J* = 7.9, 1.0 Hz, 1H, 6-H), 7.50 (*d*, *J* = 7.3 Hz, 1H, 4-H), 6.89 (*t*, *J* = 7.7 Hz, 1H, 5-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 184.3 (C-3), 159.8 (C-2), 152.9 (C-7a), 146.4 (C-6), 124.5 (C-4), 123.9 (C-5), 119.6 (C-3a), 78.3 (C-7) ppm;
MS (ESI, MeOH): m/z (%) = 290.9 ($[M+NH_4]^+$, 30), 296.0 ($[M+Na]^+$, 100), 323.0 ($[M+NH_4+MeOH]^+$, 37), 328.0 ($[M+Na+MeOH]^+$, 72), 568.5 ($[2M+Na]^+$, 50), 600.6 ($[2M+Na+MeOH]^+$, 37), 632.4 ($[2M+Na+2MeOH]^+$, 8), 272.0 ($[M-H]^-$, 100), 303.9 ($[M-H+MeOH]^-$, 20);
analysis calcd for $C_8H_4INO_2$ (273.03): C 35.19, H 1.48, N 5.13; found C 35.01, H 1.61, N 4.94.

6-Fluoroisatin (15g)
Compound **15g** (2.93 g, 59%) was obtained as a yellow solid; R_F = 0.29 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3); mp = 197–199°C (lit.: [27] 195–196°C);
MS (ESI, MeOH): m/z (%) = 166.1 ($[M+H]^+$, 68), 188.0 ($[M+Na]^+$, 84), 197.8 ($[M+H+MeOH]^+$, 100), 220.0 ($[M+Na+MeOH]^+$, 24), 228.8 ($[M+Na+MeCN]^+$, 98), 260.6 ($[M+Na+MeOH+MeCN]^+$, 21), 352.8 ($[2M+Na]^+$, 61), 164 ($[M-H]^-$, 100).

7-Fluoroisatin (15h)
Compound **15h** (1.31 g, 51%) was obtained as a brown solid; R_F = 0.23 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 193–195°C;
IR (KBr): *v* = 3440*m*, 3424*m*, 3196*m*, 3102*m*, 3058*m*, 1742*vs*, 1638*vs*, 1602*m*, 1560*w*, 1540*w*, 1496*s*, 1454*m*, 1404*w*, 1326*s*, 1286*m*, 1260*s*, 1228*m*, 1206*s*, 1158*m*, 1114*w*, 1080*w*, 1054*m*, 1034*m*, 1002*m*, 778*m*, 704*m*, 582*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 206 (3.66), 237 (3.66), 294 (3.26) nm;
^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.52 (*s*, 1H, NH), 7.52 (*ddd*, *J* = 10.4, 8.3, 1.0 Hz, 1H, 6-H), 7.36 (*ddd*, *J* = 7.4, 1.7, 0.8 Hz, 1H, 4-H), 7.06 (*ddd*, *J* = 8.3, 7.5, 4.3 Hz, 1H, 5-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 183.2 (*d*, *J* = 4.3 Hz, C-3), 159.2 (*s*, C-2), 147.2 (*d*, *J* = 245.2 Hz, C-7), 137.4 (*d*, *J* = 13.3 Hz, C-7a), 124.7 (*d*, *J* = 17.5 Hz, C-6), 123.4 (*d*, *J* = 5.4 Hz, C-5), 120.6 (*d*, *J* = 3.3 Hz, C-4), 120.5 (*d*, *J* = 3.9 Hz, C-3a) ppm; ^{19}F NMR (470 MHz, DMSO-d_6): δ = -133.06 (*dd*, *J* = 10.5, 4.3 Hz) ppm;
MS (ESI, MeOH): m/z (%) = 166.4 ($[M+H]^+$, 7), 188.1 ($[M+Na]^+$, 75), 220.1 ($[M+Na+MeOH]^+$, 58), 164.0 ($[M-H]^-$, 28);
analysis calcd for $C_8H_4FNO_2$ (165.12): C 58.19, H 2.44, N 8.48; found C 57.86, H 2.63, N 8.52.

6,7-Difluoroisatin (15i)
Compound **15i** (2.69 g, 92%) was obtained as an orange solid; R_F = 0.41 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 154–159°C;

IR (KBr): *v* = 3466*m*, 3428*w*, 3182*s*, 3122*m*, 3078*m*, 2824*m*, 2640*w*, 1758*vs*, 1742*vs*, 1702*m*, 1638*vs*, 1612*s*, 1558*m*, 1520*vs*, 1458*s*, 1418*m*, 1398*m*, 1384*m*, 1342*vs*, 1292*s*, 1272*s*, 1248*s*, 1224*m*, 1198*s*, 1158*s*, 1090*m*, 1044*s*, 992*m*, 936*m*, 902*s*, 870*m*, 842*s*, 796*m*, 786*m*, 744*m*, 704*s*, 654*s*, 606*s*, 544*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 209 (3.89), 239 (3.89), 294 (3.19), 296 (3.89), 390 (3.19) nm;
^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.80 (*s*, 1H, NH), 7.45 (*dd*, *J* = 8.3, 4.8 Hz, 1H, 4-H), 7.08 (*ddd*, *J* = 11.1, 8.2, 6.9 Hz, 1H, 5-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 181.6 (*d*, *J* = 3.7 Hz, C-3), 159.4 (C-2), 155.7 (*dd*, *J* = 255.4, 10.0 Hz, C-6), 139.6 (*dd*, *J* = 9.5, 4.9 Hz, C-7a), 135.8 (*dd*, *J* = 249.0, 16.9 Hz, C-7), 122.2 (*dd*, *J* = 10.0, 3.7 Hz C-4), 116.4 (*t*, *J* = 2.8 Hz, C-3a), 110.6 (*d*, *J* = 19.5 Hz, C-5) ppm; ^{19}F NMR (470 MHz, DMSO-d_6): δ = -124.45 (*ddd*, *J* = 21.0, 11.1, 4.8 Hz, F_6), -157.62 (*dd*, *J* = 20.9, 6.6, Hz, F_7) ppm;
MS (ESI, MeOH): m/z (%) = 206.0 ([M+Na]$^+$, 46), 237.9 ([M+MeOH]$^+$, 24), 388.8 ([2M+Na]$^+$, 13), 182.1 ([M-H]$^-$, 100), 213.9 ([M-H+MeOH]$^-$, 11); analysis calcd for $C_8H_3F_2NO_2$ (183.11): C 52.47, H 1.65, N 7.65; found C 52.21, H 1.79, N 7.50.

4,5-Dimethylisatin (15j)
Compound **15j** (1.05 g, 21%) was obtained as a reddish-brown solid; R_F = 0.23 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 220–222°C (lit.:[25] 217–218°C);
MS (ESI, MeOH): m/z (%) = 176.1 ([M+H]$^+$, 27), 193.0 ([M+NH_4]$^+$, 100), 198.1 ([M+Na]$^+$, 30), 372.9 ([2M+Na]$^+$; 100), 174.1 ([M-H]$^-$, 100.

5,6-Dimethylisatin (15k)
Compound **15k** (1.57 g, 32%) was obtained as a red solid; R_F = 0.21 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3); mp = 213–214°C (lit.:[28] 214–215°C); MS (ESI, MeOH): m/z (%) = 176.1 ([M+H]$^+$, 13), 193.0 ([M+NH_4]$^+$, 36), 198.1 ([M+Na]$^+$, 9), 370.0 ([2M+NH_4]$^+$, 14), 372.9 ([2M+Na]$^+$, 100), 404 ([2M+Na+MeOH]$^+$, 6), 174.1 ([M-H]$^-$, 100).

4-Bromoisatin (15l)
Compound **15l** (3.93 g, 57%) was obtained as an orange solid; R_F = 0.20 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 266–269°C (lit.: [29] 258–259°C);
MS (ESI, MeOH): m/z (%) = 228.0 ([M+H]$^+$, 10), 243.0 ([M+NH_4]$^+$, 41), 248.0 ([M+Na]$^+$, 100), 274.9 ([M+NH_4+MeOH]$^+$, 85), 279.9 ([M+Na+MeOH]$^+$, 67), 474.7 ([2M+Na]$^+$, 79), 506.7 ([2M+Na+MeOH]$^+$, 49), 538.7 ([2M+Na+2MeOH]$^+$, 27), 226.0 ([M-H]$^-$, 100), 255.9 ([M-H+MeOH]$^-$, 19), 260.0 ([M+^{35}Cl]$^-$, 18), 450.5 ([2M-H]$^-$, 19).

6-Bromoisatin (15m)
Compound **15m** (1.74 g, 25%) was obtained as an orange solid; R_F = 0.36 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 269–271°C (lit.: [30] 272.5°C);
MS (ESI, MeOH): m/z (%) = 228.2 ([M+H]$^+$, 8), 242.9 ([M+NH_4]$^+$, 46), 248.0 ([M+Na]$^+$, 100), 257.8 ([M+H+MeOH]$^+$, 10), 265.7 ([M+Na+H_2O]$^+$, 12), 274.8 ([M+NH_4+MeOH]$^+$, 40), 279.9 ([M+Na+MeOH]$^+$, 41), 224.0 ([M-H]$^-$, 100), 241.9 ([M-H+H_2O]$^-$, 11), 255.9 ([M-H+MeOH]$^-$, 4).

7-Bromoisatin (15n)
Compound **15n** (2.91 g, 83%) was obtained as a reddish-brown solid; R_F = 0.41 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 196–198°C (lit.: [31] 195–200°C);
MS (ESI, MeOH): m/z (%) = 243.2 ([M+NH_4]$^+$, 17), 250.0 ([M+Na]$^+$, 94), 275.0 ([M+NH_4+MeOH]$^+$, 43), 280.0 ([M+Na+MeOH]$^+$, 100), 224.0 ([M-H]$^-$, 100), 303.9 ([M+^{79}Br]$^-$, 10).

5-Bromoisatin (15o)
Compound **15o** (0.71 g, 93%) was obtained as an orange solid; R_F = 0.23 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 253–255°C (lit.: [32] 254–255°C);
ESI-MS (MeOH): m/z (%) = 224.0 ([M-H]$^-$, 83), 257.9 ([M-H+MeOH]$^-$, 7).

5-Iodoisatin (15p)
Compound **15p** (0.25 g, 17%) was obtained as a brownish solid; R_F = 0.22 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 260–262°C (lit.: [26] 254–259°C);
MS (ESI, MeOH): m/z (%) = 296.0 ([M+Na]$^+$, 93), 323.2 ([M+NH_4+MeOH]$^+$, 47), 327.9 ([M+Na+MeOH]$^+$, 100), 568.5 ([2M+Na]$^+$, 22), 600.7 ([2M+Na+MeOH]$^+$, 11), 271.9 ([M-H]$^-$, 100), 303.8 ([M-H+MeOH]$^-$, 26), 307.7 ([M+^{35}Cl]$^-$, 11), 544.5 ([2M-H]$^-$, 26).

5,6-Dimethoxyisatin (15q)
Compound **15q** (2.31 g, 68%) was obtained as a brown solid; R_F = 0.22 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 180-183°C (lit.: [33] 180–195°C);
MS (ESI, MeOH): m/z (%) = 208.1 ([M+H]$^+$, 100), 230.1 ([M+Na]$^+$, 82), 235.7 ([2M+Na+H+MeOH]$^{2+}$, 34), 242.8 ([2M+Ca+MeOH]$^{2+}$, 15).

5-Nitroisatin (15r)
Compound **15r** (0.08 g, 89%) was obtained as a yellow solid; R_F = 0.22 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 165–168°C;
^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.65 (*s*, 1H, NH), 8.45 (*dd*, *J* = 8.7, 2.4 Hz, 1H, 6-H), 8.22 (*d*, *J* = 2.2 Hz, 1H, 4-H), 7.09 (*d*, *J* = 8.7 Hz, 1H, 7-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 182.3 (C-3), 159.8 (C-2), 155.2 (C-7a), 142.6 (C-3a), 133.0 (C-6), 119.6 (C-4), 118.1 (C-5), 112.5 (C-7) ppm;
MS (ESI, MeOH): m/z (%) = 193.0 ([M+H]$^+$, 100), 215.1 ([M+Na]$^+$, 81); analysis calcd for $C_8H_4N_2O_4$ (192.13): 50.01, H 2.10, N 14.58; found: C 49.73, H 2.31, N 14.37.

General procedure C
To a solution of the isatin derivative (1 eq.) in acetic acid (1 M) at 0°C, bromine (1.2 eq.) was added dropwise, so that the temperature did not 4°C [6]. The reaction mixture was stirred for 1 h at 0°C and poured on ice. The solid was filtered off, washed with water

and dried under diminished pressure followed by column purification.

5-Bromo-4-chloroisatin (16a)
Column chromatography (silica gel, *n*-hexane/ethyl acetate, 7:4) afforded **16a** (0.15 g, 45%) as a red solid; R_F = 0.29 (silica gel, *n*-hexane/ethyl acetate, 7:4);
mp = 261–264°C;
IR (ATR): *v* = 3219*w*, 1737*s*, 1604*s*, 1480*m*, 1435*m*, 1382*m*, 1269*m*, 1236*s*, 1150*m*, 1116*m*, 1043*m*, 841*m*, 824*m*, 788*m*, 688*s*, 665*s*, 602*s*, 552*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 219 (4.06), 250 (3.95), 309 (3.06) nm; ^{1}H NMR (400 MHz, DMSO-d_6): *δ* = 11.27 (*s*, 1H, NH), 7.89 (*d*, *J* = 8.4 Hz, 1H, 6-H), 6.82 (*d*, *J* = 8.4 Hz, 1H, 7-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): *δ* = 180.3 (C-3), 158.3 (C-2), 151.1 (C-7a), 141.3 (C-6), 130.8 (C-4), 116.4 (C-5), 115.3 (C-3a), 112.5 (C-7) ppm;
MS (ESI, MeOH): m/z (%) = 283.9 ([M+Na]$^+$, 71), 308.8 ([M+NH_4+MeOH]$^+$, 29), 315.9 ([M+Na+MeOH]$^+$, 100), 259.9 ([M-H]$^-$, 100), 291.8 ([M-H+MeOH]$^-$, 12);
analysis calcd for $C_8H_3BrClNO_2$ (260.47): C 36.89, H 1.16, N 5.38; found C 36.50, H 1.37, N 5.06.

5-Bromo-6-chloroisatin (16b)
Column chromatography (silica gel, *n*-hexane/ethyl acetate, 7:4) afforded **16b** (0.06 g, 18%) as an orange solid; R_F = 0.38 (silica gel, *n*-hexane/ethyl acetate, 7:4); mp = 260–263°C;
IR (ATR): *v* = 3276*w*, 2923*w*, 1768*m*, 1737*s*, 1602*s*, 1449*m*, 1408*m*, 1261*m*, 1159*m*, 1092*m*, 972*m*, 901*m*, 863*m*, 702*m*, 662*s*, 616*s*, 573*m*, 457*s* cm^{-1};
UV-vis (MeOH): λ (log ε) = 219 (4.62), 257 (4.38), 301 (3.62) nm; ^{1}H NMR (500 MHz, DMSO-d_6) *δ* = 10.38 (s, 1H, NH), 7.00 (s, 1H, 4-H), 6.26 (s, 1H, 7-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 182.1 (C-3), 159.1 (C-2), 150.2 (C-7a), 141.5 (C-6), 129.1 (C-4), 118.4 (C-5), 114.4 (C-3a), 113.9 (C-7) ppm;
MS (ESI, MeOH): m/z (%) = 259.9 ([M-H]$^-$; 100), 291.87 ([M-H+MeOH]$^-$, 7);
analysis calcd for $C_8H_3BrClNO_2$ (260.47): C 36.89, H 1.16, N 5.38; found C 36.57, H 1.38, N 5.11.

5-Bromo-4-iodoisatin (16c)
Column chromatography (silica gel, *n*-hexane/ethyl acetate, 7:4) afforded **16c** (0.17 g, 68%) as a red solid; R_F = 0.35 (silica gel, *n*-hexane/ethyl acetate, 7:4);
mp = 220–223°C;
IR (ATR): *v* = 3143*w*, 1738*s*, 1600*s*, 1570*s*, 1467*m*, 1424*m*, 1392*w*, 1314*m*, 1245*s*, 1157*m*, 1132*m*, 1105*m*, 1051*m*, 856*m*, 831*w*, 782*s*, 773*m*, 668*s*, 644*m*, 560*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 205 (4.05), 229 (4.08), 322 (2.99), 421 (2.77) nm; ^{1}H NMR (400 MHz, DMSO-d_6): *δ* = 11.08 (s, 1H, NH), 7.82 (*d*, *J* = 8.3 Hz, 1H, 6-H), 6.85 (*d*, *J* = 8.3 Hz, 1H, 7-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): *δ* = 182.6 (C-3), 159.2 (C-2), 153.2 (C-7a), 138.9 (C-6), 124.5 (C-3a), 122.5 (C-5), 112.2 (C-7), 101.3 (C-4) ppm;
MS (ESI, MeOH): m/z (%) = 349.9 ([^{79}M-H]$^-$, 100);
analysis calcd for $C_8H_3BrINO_2$ (351.93): C 27.30, H 0.84, N 3.98; found C 27.03, H 1.11, N 3.61.

5-Bromo-6-iodoisatin (16d)
Column chromatography (silica gel, *n*-hexane/ethyl acetate, 7:3) afforded **16d** (0.22 g, 82%) as an orange solid; R_F = 0.30 (silica gel, *n*-hexane/ethyl acetate 7:3); mp = 263–265°C;
IR (ATR): *v* = 3449*w*, 3281*m*, 1736*m*, 1589*m*, 1332*s*, 1238*m*, 1152*m*, 1076*w*, 1046*w*, 899*m*, 859*m*, 821*m*, 719*m*, 657*s*, 564*s* cm^{-1};
UV-vis (MeOH): λ (log ε) = 316 nm (3.15);
^{1}H NMR (500 MHz, DMSO-d_6) *δ* = 11.15 (s, 1H, NH), 7.75 (s, 1H, 4-H, 7.46 (s, 1H, 7-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ* = 182.7 (C-3), 159.0 (C-2), 149.2 (C-7a), 127.0 (*C-4*), 123.2 (C-7), 122.0 (C-7), 119.5 (C-3a), 113.7 (C-6) ppm;
MS (ESI, MeOH): m/z (%) = 349.9 ([^{79}M-H]$^-$, 85), 381.7 ([^{79}M-H+MeOH]$^-$, 12.5);
analysis calcd for $C_8H_3BrINO_2$ (351.93): C 27.30, H 0.84, N 3.98; found C 27.07, H 1.14, N 3.68.

5-Bromo-7-chloroisatin (16e)
Compound **16e** (0.23 g, 82%) was obtained as an orange solid; R_F = 0.47 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 210–213°C;
IR (KBr): *v* = 3432*br*, 3102*m*, 1744*vs*, 1614*s*, 1456*s*, 1432*m*, 1384*w*, 1290*m*, 1270*w*, 1218*w*, 1170*m*, 1112*w*, 1072*w*, 1036*w* cm^{-1};
UV-vis (MeOH): λ (log ε) = 217 (4.13), 257 (4.13), 305 (3.13) nm;
^{1}H NMR (500 MHz, DMSO-d_6): *δ* = 11.58 (s, 1H, NH), 7.94 (*d*, *J* = 1.9 Hz, 1H, 4-H), 7.65 (*d*, *J* = 1.8 Hz, 1H, 6-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): *δ* = 182.2 (C-3), 159.3 (C-2), 146.9 (C-7a), 138.5 (C-6), 125.6 (C-4), 121.1 (C-3a), 117.4 (C-7), 114.3 (C-5) ppm;
MS (ESI, MeOH): m/z (%) = 259.9 ([M-H]$^-$, 100), 291.8 ([M-H+MeOH]$^-$, 21);
analysis calcd for $C_8H_3BrClNO_2$ (260.47): C 36.89, H 1.16, N 5.38; found C 36.77, H 1.37, N 5.16.

5-Bromo-7-iodoisatin (16f)
Compound **16f** (0.24 g, 96%) was obtained as an orange solid; R_F = 0.45 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 257–260°C;
IR (KBr): *v* = 3422*br*, 3228*br*, 1774*vs*, 1750*vs*, 1740*vs*, 1608*s*, 1458*s*, 1448*vs*, 1420*m*, 1376*m*, 1302*m*, 1264*w*, 1214*w*, 1156*m*, 1076*m*, 1032*m*, 876*m*, 690*m*, 668*m*, 544*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 203 (4.29), 288 (4.29), 359 (4.29), 313 (3.29) nm;
^{1}H NMR (400 MHz, DMSO-d_6): *δ* = 11.12 (*s*, 1H, NH), 8.13 (*d*, *J* = 1.9 Hz, 1H, 6-H), 7.66 (*d*, *J* = 1.7 Hz, 1H, 4-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): *δ* = 183.2 (C-3), 159.5 (C-2), 152.0 (C-7a), 146.7 (C-6), 126.2 (C-4), 120.7 (C-3a), 114.9 (C-5), 79.9 (C-7) ppm;
MS (ESI, MeOH): m/z (%) = 349.9 ([M-H]$^-$, 100), 382.4 ([M-H+MeOH]$^-$, 29); analysis calcd for $C_8H_3BrINO_2$ (351.93): C 27.30, H 0.84, N 3.98; found C 27.11, H 1.07, N 3.78.

5-Bromo-6-fluoroisatin (16g)
Compound **16g** (0.236 g, 75%) was obtained as an orange solid; R_F = 0.35 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 239–242°C;
IR (KBr): *v* = 3448*br*, 3196*m*, 3104*w*, 3066*w*, 1766*s*, 1750*vs*, 1736*s*, 1718*s*, 1624*vs*, 1478*m*, 1442*m*, 1380*w*, 1328*s*, 1278*m*, 1234*m*, 1212*w*, 1172*s*, 1090*w*, 1010*m*, 904*m*, 886*m*, 746*m*, 676*m*, 660*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 212 (4.10), 251 (4.10), 406 (3.10) nm;
^{1}H NMR (500 MHz, DMSO-d_6): *δ* = 11.28 (s, 1H, NH), 7.87 (*d*, *J* = 7.0 Hz, 1H, 4-H), 6.92 (d, *J* = 8.9 Hz, 1H, 7-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): *δ* = 181.9 (*d*, *J* = 1.2 Hz, C-3), 163.9 (*d*, *J* = 255.0 Hz, C-6), 159.7 (s, C-2), 152.5 (*d*, *J* = 13.0 Hz, C-7a), 130.3 (*d*, *J* = 3.1 Hz, C-4), 116.4 (*d*, *J* = 3.0 Hz, C-3a), 110.1 (*d*, *J* = 23.5 Hz, C-5), 102.1 (*d*, *J* = 28.3 Hz, C-7) ppm; ^{19}F NMR (470 MHz, DMSO-d_6): δ = -91.66 (*dd*, *J* = 8.8, 6.9 Hz) ppm;
MS (ESI, MeOH): m/z (%) = 242 ([^{79}M-H]$^-$), 274 ([^{79}M-H+MeOH]$^-$);
analysis calcd for $C_8H_3BrFNO_2$ (244.02): C 39.38, H 1.24, N 5.74; found C 39.16, H 1.45, N 5.55.

5-Bromo-7-fluoroisatin (16h)
Column chromatography (silica gel, *n*-hexane/ethyl acetate, 7:3) gave compound **16h** (0.012 g, 4%) as an amorphous brown solid; R_F = 0.37 (silica gel, *n*-hexane/ethyl acetate, 7:3); mp = 219–222°C;
^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.66 (s, 1H, NH), 7.87 (*dd*, *J* = 9.7, 1.7 Hz, 1H, 6-H), 7.56 (*d*, *J* = 1.4 Hz, 1H, 4-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ* = 181.9 (*s*, C-3), 158.8 (*s*, C-2), 147.2 (*d*, *J* = 249.9 Hz, C-7), 136.8 (*d*, *J* = 13.3 Hz, C-7a), 126.9 (*d*, *J* = 20.7 Hz, C-6), 123.1 (*d*, *J* = 3.6 Hz, C-4), 121.6 (*d*, *J* = 4.3 Hz, C-3a), 113.5 (*d*, *J* = 6.8 Hz, C-5) ppm; ^{19}F NMR (470 MHz, DMSO-d_6): δ = -130.60 (*d*, *J* = 9.7 Hz, F) ppm;
MS (ESI, MeOH): m/z (%) = 242 ([^{79}M-H]$^-$);
analysis calcd for $C_8H_3BrFNO_2$ (244.02): C 39.38, H 1.24, N 5.74; found 39.11, H 1.47, N 5.63.

5,7-Dibromo-4-chloroisatin (17a)
Column chromatography (silica gel, *n*-hexane/ethyl acetate, 7:4) gave **17a** (0.018 g, 5%) as a red solid; R_F = 0.51 (silica gel, *n*-hexane/ethyl acetate, 7:4);
mp = 240–244°C;
^{1}H NMR (400 MHz, DMSO-d_6): *δ* = 11.56 (*s*, 1H, NH), 8.23 (*s*, 1H, 6-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): *δ* = 213.8 (C-3), 158.7 (C-2), 154.6 (C-7a), 149.9 (C-4), 142.2 (C-6), 130.1 (C-3a), 115.9 (C-5), 103.8 (C-7) ppm; MS (ESI, MeOH): m/z (%) = 361.8 ([$^{35/79/81}$M+H]$^+$, 26), 391.9 ([$^{35/79/79}$M+Na+MeOH]$^+$, 55), 335.9 ([$^{35/79/79}$M-H]$^-$, 48), 367.7 ([$^{35/79/79}$M-H+MeOH]$^-$, 14);
analysis calcd for $C_8H_2Br_2ClNO_2$ (339.37): C 28.31, H 0.59, N 4.13; found C 28.03, H 0.86, N 4.97

5,7-Dibromo-6-chloroisatin (17b)
Column chromatography (silica gel, *n*-hexane/ethyl acetate, 7:4) gave **17b** (0.010 g, 3%) as a slightly orange solid; R_F = 0.59 (silica gel, *n*-hexane/ethyl acetate, 7:4); mp = 188–193°C;
^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.55 (s, 1H, NH), 7.90 (s, 1H, 4-H) ppm;
^{13}C NMR (125 MHz, DMSO-d_6): δ = 181.9 (C-3), 159.6 (C-2), 150.0 (C-7a), 141.0 (C-6), 127.4 (C-4), 119.2 (C-3a), 115.0 (C-5), 106.5 (C-7) ppm;
MS (ESI, MeOH): m/z (%) = 335.9 ([$^{35/79/79}$M-H]$^-$, 54), 367.7 ([$^{35/79/79}$M-H+MeOH]$^-$, 8);
analysis calcd for $C_8H_2Br_2ClNO_2$ (339.37): C 28.31, H 0.59, N 4.13; found C 28.04, H 0.76, N 4.00.

5,7-Dibromo-4-iodoisatin (17c)
Column chromatography (silica gel, *n*-hexane/ethyl acetate, 7:4) gave **17c** (0.03 g, 8%) as a red solid; R_F = 0.63 (silica gel, *n*-hexane/ethyl acetate 7:4);
mp = 234–238°C;
^{1}H NMR (400 MHz, DMSO-d_6): *δ* = 11.36 (*s*, 1H, NH), 8.12 (*s*, 1H, 6-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): *δ* = 181.5 (C-3), 158.6 (C-2), 150.3 (C-7a), 140.6 (C-6), 124.5 (C-3a), 123.5 (C-5), 105.4 (C-4), 100.0 (C-7) ppm;
MS (ESI, MeOH): m/z (%) = 427.9 ([$^{79/79}$M-H]$^-$, 44), 459.6 ([$^{79/79}$M-MeOH]$^-$, 25);
analysis calcd for $C_8H_2Br_2INO_2$ (430.82): C 22.30, H 0.47, N 3.25; found C 22.13, H 0.69, N 3.03.

5,7-Dibromo-6-iodoisatin (17d)
Column chromatography (silica gel, *n*-hexane/ethyl acetate, 7:3) afforded compound **17d** (0.011 g, 3%) as a lightly orange solid; R_F = 0.43 (silica gel, *n*-hexane/ethyl acetate 7:3); mp 225–228°C;
^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.37 (s, 1H, NH), 7.78 (s, 1H, 4-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 182.6 (C-3), 159.7 (C-2), 147.7 (C-7a), 125.3 (C-4), 123.0 (C-5), 122.2 (C-3a), 120.7 (C-7), 114.0 (C-6) ppm;
MS (ESI, MeOH): m/z (%) = 427.9 ([M-H]$^-$, 50), 459.7 ([M-H+MeOH]$^-$, 18);
analysis calcd for $C_8H_2Br2INO2$ (430.82): C 22.31, H 0.47, N 3.25; found: 21.98, H 0.74, N 3.02.

4.2.4 General procedure D
To a solution of the isatin (1 eq.) in EtOH at 35°C a solution of hydroxylammonium chloride (1.4 eq.) in water (1 mL) was added. The solution was heated to 80°C until the reaction was completed (as indicated by TLC) [7]. Upon cooling (ice) the product precipitated; it was filtered off, washed with water and dried.

4-Chloroisatin-3*Z*-oxime (18)
Compound **18a** (0.44 g, 81%) was obtained as a yellow solid; R_F = 0.25 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 231–233°C;
IR (KBr): *v* = 3244*s*, 3194*s*, 3082*m*, 3002*m*, 2936*m*, 2852*w*, 1702*vs*, 1654*w*, 1622*m*, 1600*s*, 1588*s*, 1484*m*, 1444*s*, 1426*m*, 1404*m*, 1318*m*, 1292*m*, 1250*m*, 1224*w*, 1172*s*, 1146*m*, 1072*m*, 1044*m*, 1036*m*, 972*m*, 940*m*, 770*s*, 734*m*, 722*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 210 (4.19), 228 (4.19), 254 nm (3.49), 260 (4.19), 300 (3.49) nm;
^{1}H NMR (400 MHz, DMSO-d_6): *δ* = 13.47 (*s*, 1H, NOH), 10.90 (*s*, 1H, NH), 7.29 (*t*, *J* = 8.0 Hz, 1H, 6-H), 7.04 (*d*, *J* = 8.2 Hz, 1H, 5-H), 6.81 (*d*, *J* = 7.8 Hz, 1H, 7-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6):

δ = 157.2 (C-2), 143.2 (C-3), 142.3 (C-7a), 131.6 (C-6), 127.1 (C-4), 122.9 (C-5), 116.5 (C-3a), 108.8 (C-7) ppm;
MS (ESI, MeOH): m/z (%) = 197.1 ($[M+H]^+$, 26), 219.0 ($[M+Na]^+$, 100), 314.9 ($[3M+K+H]^{2+}$, 32), 414.8 ($[2M+Na]^+$, 47), 195.0 ($[M-H]^-$, 100), 230.8 ($[M+^{35}Cl]^-$, 7), 390.6 ($[2M-H]^-$, 15);
analysis calcd for $C_8H_5ClN_2O_2$ (196.59): C 48.88, H 2.56, N 14.25; found C 48.66, H 2.75, N 13.99.

6-Chloroisatin-3*Z*-oxime (18b)
Compound **18b** (0.42 g, 66%) was obtained as a yellow solid; R_F = 0.14 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 246–250°C;
IR (KBr): *v* = 3422*m*, 3210*s*, 3178*s*, 2908*m*, 1736*vs*, 1716*s*, 1622*s*, 1508*w*, 1480*w*, 1440*m*, 1370*w*, 1340*m*, 1286*w*, 1246*w*, 1218*w*, 1186*w*, 1112*w*, 1076*m*, 1020*s*, 818*m*, 666*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 259 (4.31), 296 (4.01), 365 (3.31) nm; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.45 (*s*, 1H, NOH), 10.83 (*s*, 1H, NH), 7.92 (*d*, *J* = 8.1 Hz, 1H, 4-H), 7.06 (*dd*, *J* = 8.1, 1.9 Hz, 1H, 5-H), 6.89 (*d*, *J* = 1.9 Hz, 1H, 7-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.3 (C-2), 143.9 (C-3), 143.3 (C-7a), 136.1 (C-6), 128.2 (C-4), 121.8 (C-5), 114.7 (C-3a), 110.3 (C-7) ppm;
MS (ESI, MeOH): m/z (%) = 197.1 ($[M+H]^+$, 100), 219.1 ($[M+Na]^+$, 94), 314.1 ($[3M+H+K]^{2+}$, 13), 329.7 ($[3M+H+K+MeOH]^{2+}$, 19), 393.1 ($[2M+H]^+$, 13), 415.9 ($[2M+Na]^+$, 34), 195.0 ($[M-H]^-$, 100), 412.9 ($[2M-2H+Na]^-$, 3);
analysis calcd for $C_8H_5ClN_2O_2$ (196.59): C 48.88, H 2.56, N 14.25; found C 48.59, H 2.72, N 13.94.

4-Iodoisatin-3*Z*-oxime (18c)
Compound **18c** (0.16 g, 71%) was obtained as a yellow solid; R_F = 0.26 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 234–236°C;
IR (KBr): *v* = 3266*s*, 3168*s*, 3128*s*, 3074*s*, 3048*m*, 3014*m*, 2900*m*, 2838*m*, 2742*m*, 2690*m*, 2564*w*, 1704*vs*, 1620*m*, 1596*s*, 1574*s*, 1482*m*, 1436*s*, 1404*m*, 1318*s*, 1288*m*, 1258*s*, 1220*m*, 1172*s*, 1128*m*, 1114*m*, 1078*m*, 1040*s*, 960*s*, 916*m*, 764*s*, 724*m*, 702*s*, 656*m*, 638*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 204 (4.12), 237 (4.12), 258 (4.12), 313 (3.42) nm;
^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.48 (*s*, 1H, NOH), 10.78 (*s*, 1H, NH), 7.47 (*d*, *J* = 7.9 Hz, 1H, 5-H), 7.02 (*t*, *J* = 7.9 Hz, 1H, 6-H), 6.87 (*d*, *J* = 7.7 Hz, 1H, 7-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.6 (C-2), 143.2 (C-3), 142.4 (C-8), 132.8 (C-6), 131.6 (C-5), 121.4 (C-3a), 109.7 (C-7), 87.0 (C-4) ppm;
MS (ESI, MeOH): m/z (%) = 289.1 ($[M+H]^+$, 86), 311.0 ($[M+Na]^+$, 93), 342.5 ($[M+Na+MeOH]^+$, 28), 451.9 ($[3M+K+H]^+$, 43), 598.6 ($[2M+Na]^+$, 100), 287.1 ($[M-H]^-$, 100);
analysis calcd for $C_8H_5IN_2O_2$ (288.04): C 33.36, H 1.75, N 9.73; found C 33.11, H 1.92, N 9.53.

6-Iodoisatin-3*Z*-oxime (18d)
Compound **18d** (0.10 g, 57%) was obtained as a yellow solid; R_F = 0.15 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 260–262°C;
IR (KBr): *v* = 3420*m*, 3240*s*, 2906*w*, 1726*vs*, 1682*m*, 1664*m*, 1610*vs*, 1468*m*, 1428*m*, 1352*m*, 1318*m*, 1286*m*, 1246*w*, 1186*w*, 1112*m*, 1030*s*, 894*m*, 860*m*, 816*m*, 758*m*, 730*m*, 680*m*, 658*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 262 (4.17), 304 (4.17) 366 (3.47) nm;
^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.44 (*s*, 1H, NOH), 10.75 (*s*, 1H, NH), 7.69 (*d*, *J* = 7.9 Hz, 1H, 5-H), 7.40 (*d*, *J* = 7.9 Hz, 1H, 4-H), 7.21 (*s*, 1H, 7-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.1 (C-2), 143.7 (C-3), 143.6 (C-7a), 130.8 (C-5), 128.3 (C-4), 118.6 (C-7), 115.3 (C-3a), 98.6 (C-6) ppm;
MS (ESI, MeOH): m/z (%) = 289.1 ($[M+H]^+$, 100), 311.0 ($[M+Na]^+$, 85), 576.7 ($[2M+H]^+$, 23), 596.5 ($[4M+K+H]^{2+}$, 37), 598.6 ($[2M+Na]^+$, 57), 287.1 ($[M-H]^-$, 100), 596.6 ($[2M-2H+Na]^-$, 4);
analysis calcd for $C_8H_5IN_2O_2$ (288.04): C 33.36, H 1.75, N 9.73; found C 33.16, H 1.96, N 9.57.

7-Chloroisatin-3*Z*-oxime (18e)
Compound **18e** (0.30 g, 46%) was obtained as a yellow solid; R_F = 0.20 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 255–260°C (lit.: [34] 300°C);
MS (ESI, MeOH): m/z (%) = 197.1 ($[M+H]^+$, 16), 213.9 ($[M+NH_4]^+$, 15), 219.0 ($[M+Na]^+$, 30), 250.6 ($[M+Na+MeOH]^+$, 8), 392.8 ($[2M+H]^+$, 16), 414.8 ($[2M+Na]^+$, 100), 416.8 ($[M+^{37}M+Na]^+$, 66), 195.0 ($[^{35}M-H]^-$, 100).

7-Iodoisatin-3*Z*-oxime (18f)
Compound **18f** (0.39 g, 94%) was obtained as a yellow solid; R_F = 0.21 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 270–272°C;
IR (KBr): *v* = 3314*m*, 3188*s*, 3154*s*, 3074*m*, 2926*m*, 2882*m*, 2782*m*, 2658*w*, 2360*w*, 2030*w*, 1748*vs*, 1634*m*, 1604*s*, 1572*m*, 1454*m*, 1420*s*, 1386*w*, 1336*s*, 1290*w*, 1218*m*, 1172*m*, 1124*m*, 1060*w*, 1020*vs*, 790*m*, 730*m*, 682*s* cm^{-1};
UV-vis (MeOH): λ (log ε) = 228 (3.54), 235 (4.24), 254 (4.24), 260 (4.24), 304 (4.24), 372 (3.54) nm; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.51 (*s*, 1H, NOH), 10.67 (*s*, 1H, NH), 7.96 (*d*, *J* = 7.3 Hz, 1H, 4-H), 7.71 (*d*, *J* = 8.0 Hz, 1H, 6-H), 6.83 (*t*, *J* = 7.7 Hz, 1H, 5-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.7 (C-2), 145.7 (C-3), 144.7 (C-7a), 141.1 (C-6), 126.8 (C-4), 124.5 (C-5), 117.2 (C-3a), 76.2 (C-7) ppm;
MS (ESI, MeOH): m/z (%) = 289.1 ($[M+H]^+$, 84), 305.8 ($[M+NH_4]^+$, 95), 311.0 ($[M+Na]^+$, 100), 326.7 ($[M+K]^+$, 54), 342.5 ($[M+Na+MeOH]^+$, 39), 287.0 ($[M-H]^-$, 100);
analysis calcd for $C_8H_5IN_2O_2$ (288.04): C 33.36, H 1.75, N 9.73; found C 33.07, H 1.96, N 9.48.

6-Fluoroisatin-3*Z*-oxime (18g)
Compound **18g** (0.17 g, 75%) was obtained as a yellow solid; R_F = 0.15 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);

mp = 255–257°C;
IR (KBr): *v* = 3420*m*, 3174*s*, 2920*m*, 1736*vs*, 1666*m*, 1628*vs*, 1606*m*, 1496*m*, 1448*s*, 1372*s*, 1344*m*, 1328*m*, 1300*m*, 1268*w*, 1250*w*, 1234*w*, 1186*m*, 1134*s*, 1096*s*, 1022*vs*, 854*m*, 816*m*, 786*m*, 768*m*, 744*m*, 716*m*, 668*s* cm^{-1};
UV-vis (MeOH): λ (log ε) = 255 (4.19), 291 (3.89), 258 (3.19) nm;
^{1}H NMR (500 MHz, DMSO-d_6): *δ* = 13.29 (*s*, 1H, NOH), 10.83 (*s*, 1H, NH), 7.96 (*dd*, *J* = 8.4, 5.9 Hz, 1H, 4-H), 6.80 (*ddd*, *J* = 10.0, 8.4, 2.4 Hz, 1H, 5-H), 6.69 (*dd*, *J* = 9.2, 2.4 Hz, 1H, 7-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): *δ* = 164.7 (C-2), 164.0 (*d*, *J* = 248.5 Hz, C-6), 144.8 (*d*, *J* = 12.8 Hz, C-7a), 143.2 (*d*, *J* = 2.3 Hz, C-3), 129.0 (*d*, *J* = 10.3 Hz, C-4), 112.6 (*d*, *J* = 2.8 Hz, C-3a), 108.4 (*d*, *J* = 22.7 Hz, C-5), 98.5 (*d*, *J* = 27.3 Hz, C-7) ppm; ^{19}F NMR (470 MHz, DMSO-d_6)F: *δ* = -105.69 (*td*, *J* = 9.6, 5.9 Hz) ppm;
MS (ESI, MeOH): m/z (%) = 181.1 ($[M+H]^+$, 100), 197.9 ($[M+NH_4]^+$, 12), 203.0 ($[M+Na]^+$, 50), 234.5 ($[M+Na+MeOH]^+$, 10), 243.7 ($[M+Na+MeCN]^+$, 44), 360.9 ($[2M+H]^+$, 95), 382.9 ($[2M+Na]^+$, 95), 179.1 ($[M-H]^-$, 100), 236.8 ($[M-H+Na^{35}Cl]^-$, 20), 246.9 ($[M+^{35}Cl+MeOH]^-$, 20);
analysis calcd for $C_8H_5FN_2O_2$ (180.14): C 53.34, H 2.80, N 15.55; found C 53.02, H 3.05, N 15.31.

7-Fluoroisatin-3*Z*-oxime (18h)
Compound **18h** (0.41 g, 74%) was obtained as a yellow solid; R_F = 0.17 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 224–227°C;
IR (KBr): *v* = 3566*m*, 3420*m*, 3374*m*, 3210*s*, 3208*s*, 3096*s*, 2870*s*, 2646*m*, 1724*vs*, 1682*m*, 1644*s*, 1598*m*, 1496*s*, 1448*s*, 1338*s*, 294*m*, 1260*s*, 1208*s*, 1052*m*, 1022*s*, 946*s*, 796*m*, 726*m*, 714*m*, 678*s*, 588*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 236 (4.15), 246 (4.15), 292 (4.15), 324 (4.15), 333 (4.15) nm;
^{1}H-NMR (500 MHz, DMSO-d_6): *δ* = 13.53 (*s*, 1H, NOH), 11.20 (*s*, 1H, NH), 7.79 (*d*, *J* = 7.5 Hz, 1H, 4-H), 7.29 (*ddd*, *J* = 10.5, 8.5, 0.9 Hz, 1H, 6-H), 7.03 (*ddd*, *J* = 8.4, 7.6, 4.7 Hz, 1H, 5-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): *δ* = 171.9 (C-2), 164.2 (C-3), 146.3 (*d*, *J* = 242.8 Hz, C-7), 143.5 (*d*, *J* = 3.8 Hz, C-4), 129.5 (*d*, *J* = 13.2 Hz, C-7a), 123.0 (*dd*, *J* = 15.6, 4.5 Hz, C-5), 118.9 (*d*, *J* = 17.3 Hz, C-6), 118.4 (*d*, *J* = 4.4 Hz, C-3a) ppm; ^{19}F NMR (470 MHz, DMSO-d_6): *δ* = -133.06 (*dd*, *J* = 10.5, 4.7 Hz) ppm;
MS (ESI, MeOH): m/z (%) = 181.1 ($[M+H]^+$, 100), 198.0 ($[M+NH_4]^+$, 67), 203.1 ($[M+Na]^+$, 96), 219.0 ($[M+K]^+$, 13), 234.7 ($[M+Na+MeOH]^+$, 13), 179.1 ($[M-H]^-$, 100);
analysis calcd for $C_8H_5FN_2O_2$ (180.14): C 53.34, H 2.80, N 15.55; found C 53.00, H 3.13, N 15.28.

6,7-Difluoroisatin-3*Z*-oxime (18i)
Compound **18i** (0.11 g, 45%) was obtained as a yellow solid; R_F = 0.18 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 264–266°C;
IR (KBr): *v* = 3420*m*, 3410*m*, 3194*m*, 3098*m*, 3038*m*, 2926*m*, 2826*m*, 2660*w*, 2548*w*, 1744*vs*, 1698*m*, 1652*m*, 1628*s*, 1524*s*, 1446*m*, 1420*m*, 1358*s*, 1296*m*, 1270*m*, 1248*m*, 1226*m*, 1156*m*, 1046*s*, 1014*s*, 936*m*, 820*m*, 734*m*, 690*m*, 626*m* cm^{-1}; UV-vis (MeOH): λ (log ε) = 248 (4.08), 292 (4.08), 356 (3.38) nm;
^{1}H NMR (500 MHz, DMSO-d_6): *δ* = 13.54 (*s*, 1H, NOH), 11.47 (*s*, 1H, NH), 7.78 (*ddd*, *J* = 8.5, 4.7, 1.3 Hz, 1H, 4-H), 7.01 (*ddd*, 11.4, 8.3, 7.2 Hz, 1H, 5-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): *δ* = 164.3 (C-2), 151.8 (*dd*, *J* = 249.1, 10.0 Hz, C-6), 142.7 (*t*, *J* = 3.0 Hz, C-3), 135.1 (*dd*, *J* = 246.5, 17.1 Hz, C-7), 131.6 (*dd*, *J* = 9.5, 4.0 Hz, C-7a), 123.7 (*dd*, *J* = 8.5, 3.7 Hz, C-4), 114.3 (*t*, *J* = 3.0 Hz, C-3a), 109.8 (*d*, *J* = 18.7 Hz, C-5) ppm; ^{19}F NMR (470 MHz, DMSO-d_6)H: *δ* = -132.86 (*ddd*, *J* = 21.4, 11.5, 4.7 Hz, F_6), -157.46 (*ddd*, 3*J* = 21.5, 7.2, 1.5 Hz, F_7) ppm;
MS (ESI, MeOH): m/z (%) = 199.0 ($[M+H]^+$, 16), 215.9 ($[M+NH_4]^+$, 27), 221.0 ($[M+Na]^+$, 64), 415.9 ($[4M+K+H]^{2+}$, 53), 418.8 ($[2M+Na]^+$, 100), 197.1 ($[M-H]^-$, 100), 416.9 ($[2M-2H+Na]^-$, 10);
analysis calcd for $C_8H_4F_2N_2O_2$ (166.13): C 57.83, H 2.43, N 16.87; found C 57.61, H 2.68, N 16.64.

4,5-Dimethylisatin-3*Z*-oxime (18j)
Compound **18j** (0.17 g, 64%) was afforded as a yellow solid; R_F = 0.11 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 264–266°C;
IR (KBr): *v* = 3448*s*, 3422*s*, 3198*s*, 3058*m*, 2922*m*, 2878*m*, 1700*vs*, 1624*s*, 1560*w*, 1458*m*, 1386*w*, 1336*w*, 1298*w*, 1252*w*, 1194*w*, 1112*m*, 1036*m*, 1016*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 254 (4.09), 259 (4.09), 300 (4.09), 379 (3.39 nm;
^{1}H NMR (500 MHz, DMSO-d_6): *δ* = 13.10 (s, 1H, NOH), 10.49 (s, 1H, NH), 7.70 (s, 1H, 6-H), 6.67 (s, 1H, 7-H), 2.20 (s, 3H, 4`-H), 2.15 (s, 3H, 5´-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): *δ* = 165.3 (C-3), 144.8 (C2), 141.4 (C-7a), 141.3 (C-4), 130.0 (C-5), 128.3 (C-6), 114.3 (C-3a), 111.9 (C-7), 20.7 (C-5´), 19.4 (C-4´) ppm;
MS (ESI, MeOH): m/z (%) = 191.1 ($[M+H]^+$, 75), 213.1 ($[M+Na]^+$, 67), 305.1 ($[3M+K+H]^+$, 12), 320.7 ($[3M+K+H+MeOH]^{2+}$, 6), 380.9 ($[2M+H]^+$, 20), 400.0 ($[4M+K+H]^{2+}$, 25), 402.9 ($[2M+Na]^+$, 100), 189.1 ($[M-H]^-$, 100), 401.1 ($[2M+2H+Na]^-$, 10);
analysis calcd for $C_{10}H_{10}N_2O_2$ (190.20): C 63.15, H 5.30, N 14.73; found C 62.87, H 5.56, N 14.47.

5,6-Dimethylisatin-3*Z*-oxime (18k)
Compound **18k** (0.16 g, 74%) was obtained as an orange solid; R_F = 0.13 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 269–272°C;
IR (KBr): *v* = 3196*s*, 3054*s*, 2972*m*, 2948*m*, 2920*m*, 2880*m*, 1702*vs*, 1622*s*, 1458*s*, 1430*m*, 1392*m*, 1374*m*, 1334*m*, 1296*w*, 1250*w*, 1194*m*, 1168*w*, 1112*m*, 1034*m*, 1014*s*, 988*m*, 828*m*, 816*m*, 780*m*, 732*m*, 672*m*, 638*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 254 (4.36), 259 (4.36), 300 (4.36), 383 (3.36) nm;
^{1}H NMR (400 MHz, DMSO-d_6): *δ* = 13.03 (*s*, 1H, NOH), 10.49 (*s*, 1H, NH), 7.72 (*s*, 1H, 4-H), 6.66 (*s*, 1H, 7-H), 2.22 (*s*, 3H, 6´-H), 2.16 (*s*, 3H, 5´-H)) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.7 (C-2), 144.3 (C-3), 140.9 (C-7a), 140.8 (C-6), 129.4 (C-5), 127.8 (C-4), 113.8 (C-3a), 111.3 (C-7), 20.2 (C-6´), 18.9 (C-5´) ppm;
MS (ESI, MeOH): m/z (%) = 191.1 ([M+H]$^+$, 99), 213.1 ([M+Na]$^+$, 68), 305.1 ([3M+K+H]$^+$, 13), 320.7 ([3M+K+H+MeOH]$^{2+}$, 12), 380.9 ([2M+H]$^+$, 29), 400.0 ([4M+K+H]$^{2+}$, 44), 402.9 ([2M+Na]$^+$, 100), 189.1 ([M-H]$^-$, 100), 400.9 ([2M+2H+Na]$^-$, 8); analysis calcd for $C_{10}H_{10}N_2O_2$ (190.20): C 63.15, H 5.30, N 14.73; found C 62.96, H 5.58, N 14.42.

4-Bromoisatin-3*Z*-oxime (18l)
Compound **18l** (0.28 g, 85%) was obtained as a yellow solid; R_F = 0.23 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3); mp = 230–232°C (lit.: [35] 234–236°C);
MS (ESI, MeOH): m/z (%) = 241.1 ([M+H]$^+$, 78), 263.1 ([M+Na]$^+$, 100), 239.1 ([M-H]$^-$, 100), 274.9 ([M+^{35}Cl]$^-$, 29).

6-Bromoisatin-3*Z*-oxime (18m)
Compound **18m** (0.16 g, 78%) was obtained as a yellow solid; R_F = 0.15 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 224–226°C;
IR (KBr): *v* = 3384*s*, 3220*s*, 3178*s*, 2900*m*, 2864*m*, 1726*vs*, 1616*vs*, 1508*m*, 1474*m*, 1438*s*, 1372*m*, 1336*m*, 1294*w*, 1278*w*, 1244*w*, 1212*w*, 1188*w*, 1112*w*, 1062*w*, 1018*s*, 860*m*, 816*m*, 664*m* cm^{-1};
UV-vis (MeOH): λ (log ε) = 261 (4.29), 297 (3.00), 364 (3.29) nm;
^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.47 (*s*, 1H, NOH), 10.81 (*s*, 1H, NH), 7.85 (*d*, *J* = 8.1 Hz, 1H, 4-H), 7.21 (*d*, *J* = 8.1 Hz, 1H, 5-H), 7.02 (*s*, 1H, 7-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.2 (C-2), 144.9 (C-3), 143.4 (C-7a), 128.4 (C-6), 124.8 (C-4), 124.7 (C-5), 114.9 (C-3a), 113.1 (C-7) ppm;
MS (ESI, MeOH): m/z (%) = 243.1 ([^{81}M+H]$^+$, 78), 265.0 ([^{81}M+Na]$^+$, 100), 504.7 ([2^{81}M+Na]$^+$, 49), 239.0 ([^{79}M-H]$^-$, 100), 502.7 ([2^{79}M-2H+Na]$^-$, 5); analysis calcd for $C_8H_5BrN_2O_2$ (241.04): C 39.86, H 2.09, N 11.62; found C 39.64, H 2.21, N 11.37.

7-Bromoisatin-3*Z*-oxime (18n)
Compound **18n** (0.44 g, 82%) was obtained as a yellow solid; R_F = 0.20 (silica gel, toluene/*n*-heptane/ethyl acetate/formic acid, 80:20:10:3);
mp = 260–264°C;
IR (KBr): *v* = 3178*s*, 3156*s*, 3072*s*, 2892*m*, 2878*m*, 2790*m*, 1732*vs*, 1634*m*, 1616*vs*, 1580*m*, 1472*m*, 1454*m*, 1428*s*, 1342*s*, 1294*w*, 1224*m*, 1172*s*, 1134*m*, 1044*s*, 816*m*, 790*m*, 728*m*, 690*s* cm^{-1};
UV-vis (MeOH): λ (log ε) = 227 (3.49), 244 (3.49), 256 (4.19), 298 (3.49), 372 (3.49) nm;
^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.56 (*s*, 1H, NOH), 10.98 (*s*, 1H, NH), 7.95 (*d*, *J* = 7.4 Hz, 1H, 6-H), 7.55 (*d*, *J* = 8.2 Hz, 1H, 4-H), 6.98 (*dd*, *J* = 8.2, 7.5 Hz, 1H, 5-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.2 (C-2), 143.8 (C-3), 141.7 (C-7a), 134.5 (C-6), 125.9 (C-4), 123.7 (C-5), 117.5 (C-3a), 102.6 (C-7) ppm;
MS (ESI, MeOH): m/z (%) = 241.1 ([^{79}M+H]$^+$, 100), 257.9 ([^{79}M+NH$_4$]$^+$, 99), 263.0 ([^{79}M+Na]$^+$, 96), 294.6 ([^{79}M+Na+MeOH]$^+$, 25), 239.0 ([^{79}M-H]$^-$, 100);
analysis calcd for $C_8H_5BrN_2O_2$ (241.04): C 39.86, H 2.09, N 11.62; found C 39.51, H 1.96, N 11.42.

5. Molecular Modelling

Crystal structure of the *ee*AChE (PDB = 1C2O) was retrieved from protein databank (rscb.org). The enzyme was prepared according to usual procedures. Polar hydrogen atoms were added, water molecules removed, and Gasteiger charges were added. The Ligand minimisation and preparation was performed with MMFF94 force field in Datawarrior. Open Babel was used creating the pdbqt files for Autodock. Calculations were performed with Autodock4 [36]. Grid Center: 35.180, 72.374, -87.078, Grid Points 126, 126, 126 with 0.225 Angstroms spacing. Lamarckian genetic algorithm with standard GA parameters: population size = 250; number of evaluations = 25000000; number of generations 27000; GA runs = 10. Analysis of the docking poses was done with MGLTools 1.5.6; figures were created with PyMOL.

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References

1- I. Łozińska, A. Świerczyńska, Z. Molęda, A. M. Hartman, A. K. H. Hirsch, Z. Czarnocki, Donepezil-melatonin hybrids as butyrylcholinesterase inhibitors: Improving binding affinity through varying mode of linking fragments, Arch. Pharm., **2018**, 1800194.
2- P. Costanzo, L. Cariati, D. Desiderio, R. Sgammato, A. Lamberti, R. Arcone, R. Salerno, M. Nardi, M. Masullo, M. Oliverio, Design, Synthesis, and Evaluation of Donepezil-Like Compounds as AChE and BACE-1 Inhibitors, ACS Med. Chem. Lett., **2016**, 7, 470-475.
3- K. O. Yerdelen, M. Koca, B. Anil, H. Sevindik, Z. Kasap, Z. Halici, K. Turkaydin, G. Gunesacar, Synthesis of donepezil-based multifunctional agents for the treatment of Alzheimer’s disease, Bioorg. Med. Chem. Lett., **2015**, 25, 5576-5582.
4- M. Koca, K. O. Yerdelen, B. Anil, Z. Kasap, H. Sevindik, I. Ozyurek, G. Gunesacar, K. Turkaydin, Design, synthesis and biological activity of 1H-indene-2-carboxamides as multi-targeted anti-Alzheimer agents, J. Enzyme Inhib. Med. Chem., **2016**, 31, 13-23.
5- M. S. Altowyan, M. Ali, S. M. Soliman, A. M. Al-Majid, M. S. Islam, S, Yousuf, M. I. Choudhary, H. A. Ghabbour, A. Barakat, Synthesis, computational studies and biological activity of oxamohydrazide

derivatives bearing isatin and ferrocene scaffolds, J. Mol. Struct., **2020**, 1202, 127372.
6- A. V. Bogdanov, I. F. Zaripova, A. D. Voloshina, A. S. Sapunova, N. V. Kulik, I. V. Tsivunina, A. B. Dorbrynin, V. F. Mironov, J. Fluorine Chem., **2019**, 227, 109345.
7- M. M. H. Arief, W. I. A. El-Dougdoug, M. A. Sayed, Synthesis of some new isatin derivatives of expected biological activities, J. Basic Environm. Sci., **2019**, 6, 149-155.
8- T. Sandmeyer, Über Isonitrosoacetanilide und deren Kondensation zu Isatinen, Helv. Chim. Acta, **1919**, 2, 234-242.
9- Y. S. Tingare, M. T. Shen, C. Su, S. Y. Ho, S. H. Tsai, B. -R. Chen, W. R. Li, Novel Oxindole Based Sensitizers: Synthesis and Application in Dye-Sensitized Solar Cells, Org. Lett., **2013**, 15, 4292-4295.
10- J. B. Campbell, E. J. Warawa, Preparation and formulation of heterocyclic fused tricyclic compounds as anxiolytics, EP245053A119871111.
11- L. -S. Feng, M. -L. Liu, S. Zhang, Y. Chai, B. Wang, Y.-B. Zhang, K. Lv, Y. Guan, H. -Y. Guo, C. -L. Xiao, Synthesis and in vitro antimycobacterial activity of 8-OCH_3 ciprofloxacin methylene and ethylene isatin derivatives, Eur. J. Med. Chem., **2011**, 46, 341-348.
12- Z. Wang, C. Wang, Y. Sun, N. Zhang, Z. Liu, J. Liu, A novel strategy to the synthesis of 4-anilinoquinazoline derivatives, Tetrahedron, **2014**, 70, 906-913.
13- P. Polychronopoulos, P. Magiatis, A. L. Skaltsounis, V. Myrianthopoulos, E. Mikros, A. Tarricone, A. Musacchio, S.M. Roe, L. Pearl, M. Leost, P. Greengard, L. Meijer, Structural Basis for the Synthesis of Indirubins as Potent and Selective Inhibitors of Glycogen Synthase Kinase-3 and Cyclin-Dependent Kinases, J. Med. Chem., **2004**, 47, 935-946.
14- G. L. Ellman, K. D. Courtney, V. J. Andres, R. M. Featherstone, A new and rapid colorimetric determination of acetylcholinesterase activity, Biochem. Pharmacol., **1961**, 7, 88-95.
15- A. Loesche, A. Kowitsch, R. Csuk, S. D. Lucas, Z. Al-Halabi, W. Sippl, A. Al-Harrasi, Ursolic and oleanolic acid derivatives with cholinesterase inhibiting potential, Bioorg. Chem., **2018**, 85, 23-32.
16- S. Liu, W. Wei, Y. Li, X. Liu, X. Cao, K. Lei, M. Zhou, Design, synthesis, biological evaluation and molecular docking studies of phenylpropanoid derivatives as potent anti-hepatitis B virus agents, Eur. J. Med. Chem., **2015**, 95, 473-482.
17- Suresh, D. Kumar, J. S. Sandhu, Bismuth(III) Chloride–Mediated, Efficient, Solvent-Free, MWI-Enhanced Doebner Condensation for the Synthesis of (E)-Cinnamic Acids, Synth. Commun., **2010**, 40, 1915-1919.
18- T. Takahashi, M. Miyazawa, Tyrosinase inhibitory activities of cinnamic acid analogues, Pharmazie, **2010**, 65, 913-918.
19- K. Kindler, K. Lührs, Studien über den Mechanismus chemischer Reaktionen, XXII. (Über Hydrierungen und über spezifische Hydrierungen mittels gebundenen Wasserstoffs, VI). Hydrierungen mittels Terpenen, Ann. Chem., **1965**, 685, 36-48.
20- J. Koo, The Synthesis of 4,5,6-Trimethoxyindene- and 4,5,6-Trimethoxyindanecarboxylic Acids and Esters, J. Am. Chem. Soc., **1953**, 75, 1889-1891.
21- C. Pan, X. Zeng, Y. Guan, X. Jiang, L. Li, H. Zhang, Design and Synthesis of Brazilin-Like Compounds, Synlett, **2011**, 425-429.
22- T. M. Harris, C. R. Hauser, Benzylation at the Terminal Methyl Group of Certain Unsymmetrical β-Diketones Through One of Two Possible Intermediate Dicarbanions, J. Am. Chem. Soc., **1959**, 81, 1160-1164.
23- T. Dohi, N. Takenaga, A. Goto, H. Fujioka,Y. Kita, Clean and Efficient Benzylic C−H Oxidation in Water Using a Hypervalent Iodine Reagent: Activation of Polymeric Iodosobenzene with KBr in the Presence of Montmorillonite-K10, J. Org. Chem., **2008**, 73, 7365-7368.
24- A. Romeo, H. Corrodi, E. Hardegger, Umsetzungen des o-Nitrophenylessigesters und des 2-Chlor-6-nitro-phenyl-brenztraubensäureesters, Helv. Chim. Acta, **1955**, 38, 463-467.
25- S. B. Kadin, Preparation and formulation of analgesic and antiinflammatory 1,3-diacyl-2-oxindole compounds, US4690943A19870901.
26- M. E. Matheus, F. D. A. Violante, S. J. Garden, A. C. Pinto, P. D. Fernandes, Isatins inhibit cyclooxygenase-2 and inducible nitric oxide synthase in a mouse macrophage cell line, Eur. J. Pharmacol., **2007**, 556, 200-206.
27- K. C. Joshi, V. N. Pathak, S. K. Jain, Studies of potential organo-fluorine antibacterial agents. Part 5: Synthesis and antibacterial activity of some new fluorine-containing indole-2,3-dione derivatives, Pharmazie, **1980**, 35, 677-679.
28- B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, J. H. Williams, An antimalarial alkaloid from hydrangea. XV. Synthesis of 5-, 6-, 7-, and 8-derivatives with two identical substituents, J. Org. Chem., **1952**, 17, 149-156.
29- L. Ettinger, P. Friedländer, Über 6.6′-Dibrom-indirubin, Ber. Dt. Chem. Ges., **1912**, 45, 2081-2083.
30- S. Inagaki, Diphenylisatin and its derivatives. IV. Monobromo derivatives of dianisoleisatin and its oxidation product, Yakugaku Zasshi, **1938**, 58, 961-975.
31- A. Beauchard, H. Laborie, H. Rouillard, O. Lozach, Y. Ferandin, R. L. Guével, C. Guguen-Guillouzo, L. Meijer, T. Besson, V. Thiéry, Synthesis and kinase inhibitory activity of novel substituted indigoids, Bioorg. Med. Chem., **2009**, 17, 6257-6263.
32- F. Ziegler, T. Kappe, R. Salvador, Synthesen von Heterocyclen, 44. Mitt.: Eine Synthese des Isatins, Monatsh. Chem., **1963**, 94, 453-459.
33- C. A. Fetscher, M. T. Bogert, Researches on quinaolines. XLIV. The synthesis of some new quinazoline derivatives of veratrole akin to alkaloids, J. Org. Chem., **1939**, 4, 71-87.
34- J. Gray, D. R. Waring, 3-Amino-2,1-benzoisothiazole. Synthesis of some chloro and trifluoromethyl derivatives, J. Heterocycl. Chem., **1980**, 17, 65-67.
35- D. H. Klaubert, J. H. Sellstedt, C. J. Guinosso, R. J. Capetola, S. C. Bell, N-(Aminophenyl)oxamic acids and esters as potent, orally active antiallergy agents, J. Med. Chem., **1981**, 24, 742-748.
36- G. M. Morris, R. Huey, W. Lindstrom, M. F. Sanner, R. K. Belew, D. S. Goodsell, A. J. Olson, AutoDock and AutoDockTools: Automated docking with selective receptor flexibility, J. Comput. Chem., **2009**, 30, 2785-2791