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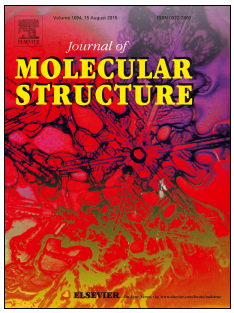

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Ana Ratković, Željko Marinić, Irena Škorić

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Flow-photochemical Synthesis of the Functionalized Benzobicyclo[3.2.1]octadiene Skeleton

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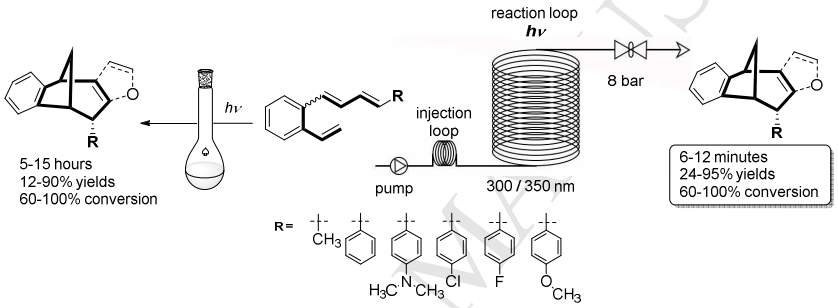
Graphical abstract



Abstract

A convenient practical home-made continuous flow-photochemistry setup was evaluated with the aim to enable a more efficient protocol for the synthesis of functionalized benzobicyclo[3.2.l]octadiene skeleton by intramolecular [2+2]-photocycloaddition reaction. Numerous compounds with the bicyclo[3.2.l]-skeleton are proven as potent inhibitors of dopamine and serotonin transporters and also play a crucial role in treatment of central nervous system and Alzheimer's disorders. The yields, reaction times and conversions gained from the flow setup were compared to those obtained from the conventional photoreactor. In comparison to the batch reaction, the flow reaction showed better results, both in increasing the isolated yield and productivity and in lowering the reaction time. This first application of the flow-photochemistry on *β*-heteroaryl-*o*-divinylbenzenes and *o*-vinylphenyl substituted butadienes proved to be more efficient and less sensitive to oxygen enabling us to scale-up the intramolecular cycloaddition without scaling-up the equipment. Additionally, for all the obtained, potentially bioactive,

derivatives promising calculated physico-chemical and absorption, distribution, metabolism, and elimination (ADME) properties were also given.

KEYWORDS: benzobicyclo[3.2.1]octadienes, continuous flow photochemistry, functionalized polycyclic skeleton, intramolecular photocycloaddition, physico-chemical and ADME properties.

1. Introduction

The bicyclo[3.2.l]octane system is a common subunit in many natural products. It is present in diterpene families of compounds such as the kaurenes and the gibberellins and also in many sesquiterpenes [1]. One of the interesting properties of the bicyclo[3.2.1]octane skeleton is that it is fairly rigid and can therefore coordinate two or more ligands and this is of great value to medicinal chemists, particularly in the search for bioactivity [2-5]. This structural moiety is the basic framework of numerous important biologically active natural compounds or their metabolites [6-8]. More importantly, compounds with the bicyclo[3.2.1]-skeleton are proving as potent inhibitors of dopamine and serotonin transporters and play a crucial role in treatment of central nervous system (CNS) and Alzheimer's disorders (Figure 1) [9,10].

Synthesis of compounds containing the bicyclo[3.2.l]octane and bicyclo[3.2.l]octadiene core are well documented in literature [11-15]. Bicyclo[3.2.l]-skeleton can be constructed using different synthetic pathways, one of which is the photochemical approach that has been developed by our group in batch photochemical reactor [16-20]. Photochemically induced organic reactions provide an important path to complex products from simple starting materials. The unsaturated bicyclo[3.2.l]octane structure can be even more useful than the saturated bicyclo[3.2.l]octane skeleton, as it can easily be transformed further by adding various functional groups to the isolated double bond. In our group, a whole library of polycylic compounds was obtained by utilization of the photochemical synthesis in the traditional photoreactor.

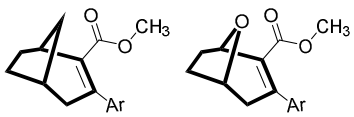


Figure 1. Examples of compounds with benzobicyclo[3.2.1]-skeleton displaying expressed CNS activities [10].

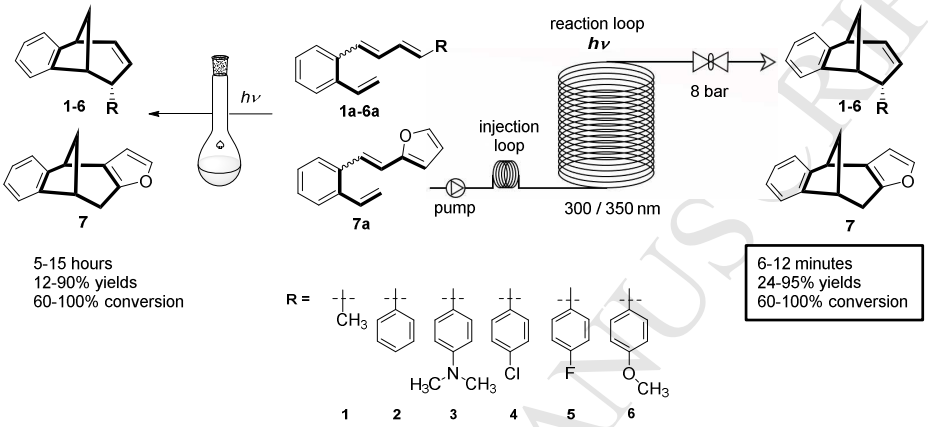
In recent years, research groups are adopting more technological solutions to enable highly automated syntheses which can help the discovery of compounds from early phases of discovery to preclinical investigations and drug production. Continuous flow systems are emerging as powerful tools in the organic synthetic community enabling highly automated synthesis. These systems have many advantages in comparison to the conventional batch methods. They are more favoured when applied in reaction screening and optimization. Continuous flow reactors have shown remarkable efficiency during screening on reaction parameters such as temperature, pressure, residence time, catalysts used, solvents [21-25]. A key advantage of such technology is the possibility to scale-up a reaction without scaling-up the equipment by exploiting the continuous flow of the reagents through the system [26-30].

Flow techniques have also been applied to synthetic organic photochemistry on a variety of important platforms [31-37]. In this work, for the first time, flow photochemistry was utilized for the synthesis of the benzobicyclo[3.2.l]octadiene skeleton. New benzobicyclo[3.2.l]octadienes were prepared using the traditional (batch) method and also in the flow reactor to explore the benefits. In comparison to the batch reaction, the flow reaction showed better results, both in increasing the yield and productivity and lowering the reaction time. We were able to perform the reactions in shorter residence times and scale-up the intramolecular [2+2]-photocycloaddition reaction obtaining the desired products without scaling-up the equipment.

2. Results and discussion

The intramolecular [2+2]-photocycloaddition reaction toward some already known (**2**, **4**, **6** and **7**) [16-19] and several novel (**1**, **3** and **5**) benzobicyclo[3.2.1]octadienes from *β*-heteroaryl-*o*-divinylbenzenes and *o*-vinylphenyl substituted butadienes (**1a**-**7a**) (Scheme 1) was performed on the traditional batch way using the Rayonet reactor with 16 lamps (300 or 350 nm, 8W lamps). The synthesis was also performed in the flow system using a convenient practical home-made flow-photochemistry setup (Figure 2) with 19 m reactor system consisting of UV transparent tubing (for leaking through the reaction mixture), wraped around the pyrex cuvette and placed in a Rayonet reactor. The flow setup was evaluated with the aim to enable a more efficient protocol for the rapid synthesis of **1**-**7**, as valuable substrates for further functionalization of their isolated double bond and/or the functionalization of the alkyl or aryl substituents on the benzobicyclo[3.2.1[octadiene core (in the case of **1**-**6**). Additionally, the targeted photoproduct **7** has two reactive double bonds incorporated into the furan ring, making it as a substrate also synthetically very interesting.

The starting materials **1a**-**7a** for the photochemical experiments were prepared by the Wittig reaction from α,α'-*o*-xylyl(ditriphenylphosphonium)dibromide and corresponding aldehydes according to the general procedure developed for the whole library of analogue [38-42]. Upon irradiation the primary photoisomerization of the mixtures of the isomers of the starting compounds **1a**-**7a** is followed by competitive stereoselective intramolecular [2+2]-photocycloaddition giving differently substituted benzobicyclo[3.2.1]octadienes **1**-**7**.



Scheme 1. Synthesis of benzobicyclo[3.2.1]octadiene derivatives **1**-**7** in a batch and flow photochemical setup.

4-substituted benzobicyclo[3.2.1]octadienes **1**-**6**, as *endo*-stereoisomers, and compound **7** were obtained as the main products, with traces of *exo*-4-substituted photoproduct (in the case of **5**) and besides high-molecular-weight material in all cases (Scheme 1). The stereoselectivity of the reaction and the preferable ring closure to *endo*-isomer of **1**-**6** have been ascribed to the stabilization of the transition state in *endo*-orientation by the attractive intramolecular interactions of the benzo-methyl/aryl groups [19]. We have chosen the derivatives **1**-**7** with diversified targeted alkyl-, phenyl- and different aryl-substituents (*p*-dimethylaminophenyl-, *p*-chlorophenyl, *p*-fluorophenyl, *p*-methoxyphenyl-) to compare their synthesis, yields, quantum yields, reaction times, residence times and productivity in batch and flow system. Also, we performed the flow photoreaction to obtain fused furan structure **7** suitable for further functionalization through oxidative cleavage of the furan ring [43].

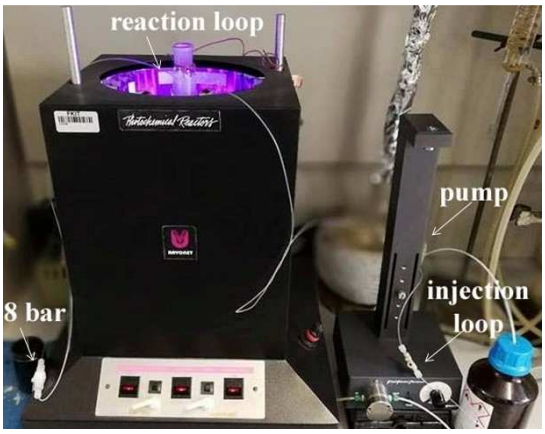


Figure 2. Home-made flow-photochemistry setup.

All irradiation experiments were performed in toluene solutions under anaerobic conditions at 300 nm (for the synthesis of **1** and **7**) and 350 nm (for the synthesis of **2-6**), depending on the absorption spectra of the starting conjugated substrates **1a-7a** (Figure 3). The preparative batch irradiation experiments of starting compounds **1a-7a** (Scheme 1) were performed at low concentrations in the order of 0.001 mmol/mL. At the same time, flow irradiation experiments were performed on the same substrates in toluene solutions using plunger pump (Flash Master Personal Argonaut) for the applied slowest possible flow rate of 0.4 mL/min to achieve the full conversion and concentration of the solutions of 0.093 mmol/mL.

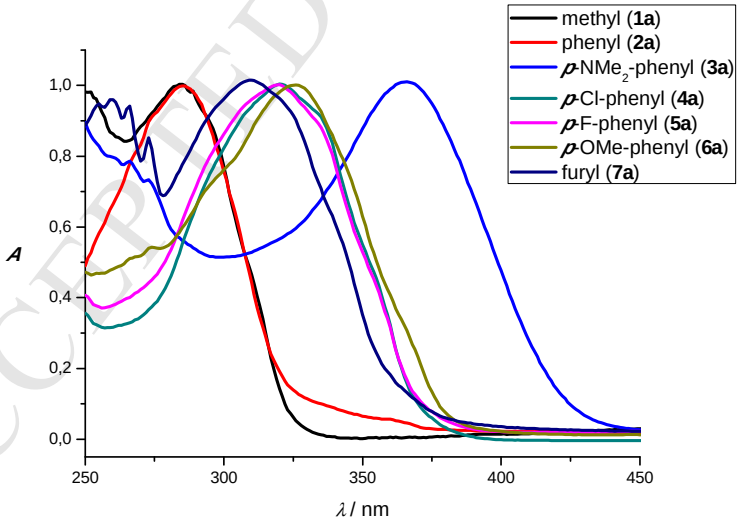


Figure 3. Normalized absorption spectra of the mixtures of isomers of starting compounds **1a-7a** used in the photochemical synthesis of **1-7**

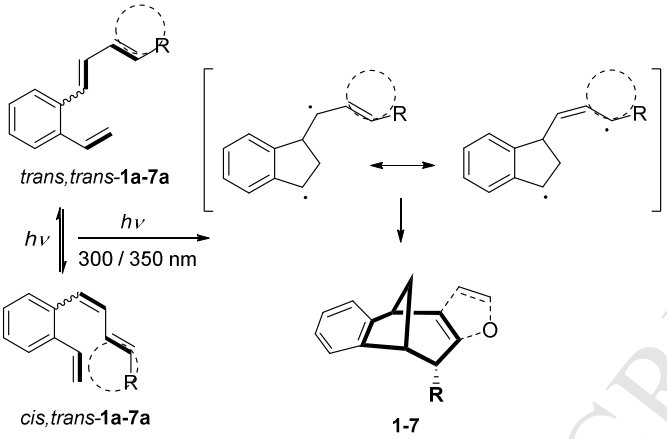
The comparison of yields of the batch and flow [2+2]-photocycloaddition is given in Table 1. Utilizing the experimental conditions for this stereoselective intramolecular cycloaddition in the

continuous flow reactor, we obtained the desired structures **1**-**7** after the residence time of only 6-12 minutes in moderate to very high yields 48-95% (with complete consumption of starting material), except for the *p*-dimethylamino derivative **3** (60% of consumption). Obviously, the tertiary amino group in the photoproduct **3** (in comparison to other molecules with two aryl groups **2**, **4**-**6**) contributes to the lower stability possibly through the lowering of the intensity of π-π interactions by competitive electronic effects. Evidently, the strong electronic effects of the *p*-dimethylamino in the starting substrate **3a** during the photocycloaddition reaction also bring to the incomplete consumption of the starting material. Besides the increase in the yields, we also achieved the significant increase of the productivity of **1**-**7** in comparison to the batch photoreaction (Table 1), especially on the photoproduct **1**.

The improvement of the productivity of **1**-**7** during the flow photochemical reaction can be explained by considering the different physical reaction parameters in two applied reactors. In addition to the benefits of flow systems derived from the fluidics approach such as enhanced heat and mass transfer, it is known that the relatively low reactor volume and especially the high surface area to volume ratio of flow reactors have proven to be key advantages for light-initiated reactions, as intense and uniform irradiation of the reaction mixture is assured. Because of the short path length of the light, higher substrate concentrations were used, and therefore, the reaction throughput was significantly increased. The light exposure is very precisely controlled by the pump flow rate, which minimizes over irradiation of the mixture, avoiding undesired side products, which were very common in our batch experiments. Due to the use of minimal solvents it is ensured that reactions are sustainable, environmentally friendly and conducted in a safe manner. Continuous flow setup (Figure 2) allowed us easy scale-up as no change in reactor size was required. It is very important to emphasize that the application of the continuous flow-photochemistry on different *β*-heteroaryl-*o*-divinylbenzenes and *o*-vinylphenyl substituted butadienes **1a**-**7a** proved to be less sensitive to the oxygen present in the solution compared to the traditional batch reaction due to the very short residence times and rapid reaction. Additionally, we were able to use higher concentrations in the flow system that are not usual for intramolecular reactions. The optimization of the reaction conditions with higher flow rates could enable further decrease in the residence time required for the full conversion of starting compounds **1a**-**7a** and further increase of the productivity.

Regarding the mechanistic considerations, the formation of benzobicyclic structures **1**-**7** could be explained by initial intramolecular cycloaddition and formation of resonance-stabilized intermediate followed by 1,6-ring closure (Scheme 2), as proposed in the photochemical reactions

of some *β*-heteroaryl substituted *o*-divinylbenzenes [16,20,38,39] and *o*-vinylphenyl substituted butadienes [17,19].



Scheme 2. Proposed mechanism of the intramolecular photocycloaddition giving the benzobicyclo[3.2.1]octadienes **1-7**.

A study of efficiency was also conducted for the batch photoreaction where the efficiency of intramolecular cycloaddition of starting compounds **1a-7a** was investigated by the use of the ferrioxalate actinometer. As it is shown in Table 1, the quantum yields of the intramolecular cycloaddition of starting conjugated systems **1a-7a** are relatively high toward the benzobicyclo[3.2.1]-skeleton. These results add even more importance to the synthesis of **1-7** by photocycloaddition. The quantum yields for the flow system is technically impossible to measure so the benefits of the continuous flow system above the batch could not be analyzed according to that base but through the improvement of the productivity.

Table 1. Photocycloaddition reaction[a] to photoproducts **1-7**.

Photo-product	Quantum yield in batch[c]	Yield for batch [%][b]	Time in batch [h]	Yield for flow [%][b]	Residence time [min]	Conversion[d] [%]	Productivity [μmol/min][e]
1	0.02	25	15	**48**	**6**	100	**0.18/39.2**
2	0.22	90[19]	5	**95**	**6**	100	**0.65/33.0**
3	0.22	12	10	**24**	**12**	60	**0.06/3.6**
4	0.23	77[17]	5	**83**	**6**	100	**0.48/25.0**
5	0.24	80	5	**87**	**6**	100	**0.53/29.0**
6	0.12	50[18]	15	**70**	**12**	100	**0.13/11.0**
7	0.22	90[16]	15	**92**	**12**	100	**0.24/14.8**

Reaction conditions: [a]The irradiation experiments in batch photoreactor and flow system were performed in toluene solutions at 300 nm (for the synthesis of compounds **1** and **7**) and 350 nm (for the synthesis of compounds **2**-**6**), depending on the absorption spectra of the starting substrates; [b]Isolated yield; Concentration of the toluene solution in the batch was in the order of 0.001 mmol/mL and for the flow 0.093 mmol/mL; Flow rate was 0.4 mL/min; [c]For calculation see Supporting Information; [d]Conversion is the same for the batch and flow system; [e]Comparison of productivity in batch/flow systems.

In this study, the structure-property relationships [44-46] with predictive models (see Supporting Information) for photoproducts **1-7** bearing the crucial benzobicyclo[3.2.1]-skeleton has been analyzed for the first time (Table 2). Physico-chemical and ADME (absorption, distribution, metabolism, and elimination) properties have been calculated specially logP, solubility, permeability across biological membranes, plasma protein binding, metabolic stability and CNS penetration. Generally, the absorption parameter shows the bioavailability, the distribution predicts where the drug is distributed, how fast and how extensive, metabolism parameter shows how fast, what mechanism, what metabolite is formed, and whether it is active or toxic, and the elimination value predicts the route to the target. It is known that fundamental physico-chemical features of CNS drugs are related to their ability to penetrate the blood-brain barrier affinity and exhibit their CNS activity. Promising structural and physico-chemical parameters identified in the current study will serve us as a useful tool, to design, filter and prioritize compounds to be synthesized further. As a more detailed investigation of acetylcholinesterase (enzyme important at early stages of Alzheimer's disease) inhibitory activity as well as the butyrylcholinesterase (enzyme important at later stages of Alzheimer's disease) inhibitory activity is underway, the CNS penetration is one of the most interesting parameters.

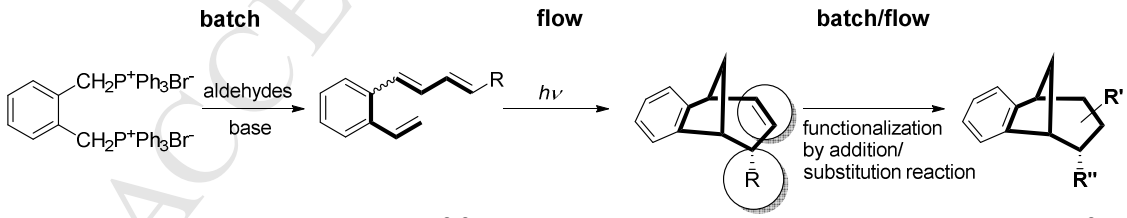
Table 2. Calculated physico-chemical and ADME properties[44] for compounds **1-7**.

Photo-product	logP	Solubility	Permeability	PPB [%]	CNS	Metabolic stability
1	**4.04**	0.005	$245e^{-6}$	**82**	**-1.77**	0.53
2	5.22	0.008	$2196e^{-6}$	95	-2.52	0.51
3	5.15	0.003	$221e^{-6}$	96	-2.48	0.53
4	5.53	0.001	$195e^{-6}$	98	-2.76	0.53
5	5.03	0.007	$228e^{-6}$	96	**-2.39**	0.51
6	4.89	0.003	$232e^{-6}$	96	-2.44	0.53
7	**3.77**	0.020	$245e^{-6}$	95	**-2.31**	0.52

As was mentioned before, some compounds having the same bicyclo[3.2.1]-core as structures **1-7** have proved to be potent inhibitors of dopamine and serotonin transporters and also play a crucial

role in treatment of CNS and Alzheimer's disorders [9,10]. Analizing the obtained calculated values (Table 2), it is evident that all photoproducts **1**-**7** show significant CNS penetration properties, especially compounds **1**, **5** and **7**, the alkyl, *p*-fluorophenyl and furyl derivative, respectively. It is important experimental result that the fluorinated photoproduct **5** also gave 100% conversion within 6 minutes in the flow system and significant CNS penetration properties in the same time, as the fluorinated compounds are currently trending in organic synthesis [47]. This derivative has a very high yield in batch and flow system and good productivity in both systems. For all photoproducts **1**-**7** *in silico* analysis were also performed showing the best CNS penetration and lipophilicity properties for structures **1**, **5** and **7**, which means that they could possess good blood-brain barrier penetration capability. Generally, the promising value of CNS penetration is between -3 and 0 (see Supporting Information). Photoproduct **1** has better CNS and plasma protein binding (PPB, Table 2) values than the other products **2**-**7**, probably because of smaller molecule with only one aryl substituent and consequently not so rigid structure (without π-π interactions between two aromatic rings). Analizing all *in silico* values, it can be concluded that bicyclo[3.2.1]octadiene structures in general show potentially good CNS activity.

The described home-made flow-photochemistry setup allowed improvement of the productivity of photoreaction products **1**-**7** strengthen this way the further purpose of this work. As it was mentioned, some compounds having the same bicyclo[3.2.1]-core as **1**-**7** have proved to be potent inhibitors of dopamine and serotonin transporters and also play a crucial role in treatment of CNS and Alzheimer's disorders (see Supporting Information) [9,10]. On the other hand, the flow-photochemical methodology could be a practical option also for further functionalization reactions of these efficiently obtained and potentially bioactive structures (Scheme 3).



Scheme 3. Schematic representation of further possible applications using the evaluated flow-photochemistry setup.

3. Conclusion

In this paper we have demonstrated a convenient practical home-made continuous flow-photochemistry setup to enable more efficient protocol for the synthesis of functionalized benzobicyclo[3.2.l]-skeleton by intramolecular [2+2]-photocycloaddition reaction. The yields, residence time and conversion of these reactions were compared to those obtained in traditional batch photoreactor. This first application of continuous flow methodology on the photochemistry of different *β*-heteroaryl-*o*-divinylbenzenes and *o*-vinylphenyl substituted butadienes proved to be much more efficient and less sensitive to oxygen compared to the traditional batch reaction, enabling us to scale-up the intramolecular cycloaddition reaction without scaling-up the equipment and allowing the improvement of the productivity of photoproducts **1-7**. The measurements of experimental physico-chemical and ADME properties, biological activity and cholinesterase inhibitory activity of the photoproducts are also currently underway proving the further purpose of this work.

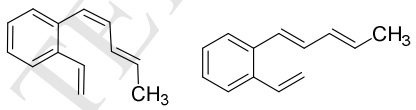
4. Experimental section

General

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-600 Spectrometer All NMR spectra were measured in $CDCl_3$ using tetramethylsilane as reference. UV spectra were measured on a Varian Cary 50 UV/VIS Spectrophotometer. Mass spectra were obtained on a GC-MS (Varian CP-3800 Gas Chromatograph-Varian Saturn 2200) equipped with FactorFour Capillary Column VF-5ms. Irradiations were performed in a quartz or pyrex cuvettes in toluene solutions using RPR 3000 Å and RPR 3500 Å lamps. All irradiation experiments were carried out in deoxygenated solutions by bubbling a stream of argon prior to irradiation. Melting points were obtained using an Original Kofler Mikroheitztisch apparatus (Reichert, Wien) and are uncorrected. HRMS analysis were carried out on a mass spectrometer (MALDI TOF/TOF analyzer), equipped with Nd:YAG laser operating at 355 nm with firing rate 200 Hz in the positive (H+) or negative (H–) ion reflector mode. Silica gel (Merck 0.063-0.2 mm) was used for chromatographic purifications. Solvents were purified by distillation. Boiling range of petroleum ether, used for chromatographic separation, was 40-70 ºC.

The starting cinnamaldehydes and furan-2-carboxaldehyde for the Wittig reaction were obtained from a commercial source. β,β'-*o*-xylyl(ditriphenylphosphonium)dibromide was synthesized from the corresponding dibromide and triphenylphosphine in benzene solution.

General procedure for synthesis of starting substrates 1a-7a used in photochemical reactions:[48] To a stirred solution of the diphosphonium salt of α,α'-o-xylenedibromide (5.5 mmol) in absolute ethanol (100 mL, 3 Å sieves), corresponding aldehydes (1.1 eq) were added. A solution of sodium ethoxide (1.1 eq in 15 mL of absolute ethanol) was added dropwise and reaction mixture stirred under nitrogen for 1h at RT. Under a stream of dry nitrogen, gaseous formaldehyde (obtained by decomposition of paraformaldehyde used in excess, (1.0 g) was introduced together with sodium ethoxide solution, which was added dropwise. The reaction mixture was stirred overnight at RT. After removal of the solvent, the residue was worked up with ice-water and extracted with toluene (5 x 30 ml). The toluene extracts were dried with anhydrous $MgSO_4$. Evaporation of solvent under reduced pressure afforded crude mixture of geometrical isomers of **1a-7a** as starting materials for the photochemical reactions to afford compounds **1-7**. The crude reaction mixture was purified and the isomers of **1a-7a** were separated by repeated column chromatography on silica gel using petroleum ether as eluent. The first fractions yielded *cis*- or *cis,trans*- and the last fractions *trans*- or *trans,trans*-isomer depending on the starting aldehydes. Characterization data of the synthesized compounds **1a-7a** are given below.

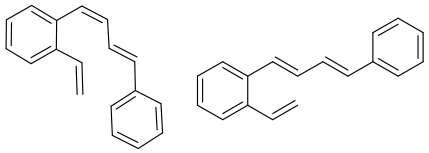


cis,trans-**1a** *trans,trans*-**1a**

1-ethenyl-2-(penta-1,3-dien-1-yl)benzene (1a): Yield 35.0%, according to ^{1}H NMR spectroscopy, a mixture of 50% *cis,trans*- and 50% of *trans,trans*-isomer. HRMS for $C_{13}H_{14}$: M^+_{calcd} 170.1157; M^+_{found} 170.1167 (for a mixture of isomers of **1a**).

cis,trans-**1a**: R_f 0.75 (petroleum ether); colourless oil; UV (EtOH) λ_{max} (log ε) 263 (4.09); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.47-7.44 (m, 1H), 7.20-7.16 (m, 3H), 6.81 (dd, 1H, *J* = 17.5; 10.5 Hz), 6.31 (d, 1H, *J* = 11.6 Hz), 6.25-6.16 (m, 2H), 5.81-5.74 (m, 1H), 5.59 (dd, 1H, *J* = 17.5; 1.3 Hz), 5.19 (dd, 1H, *J* = 11.3; 1.3 Hz), 1.67 (dd, 3H, *J* = 7.2; 1.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 136.0 (s), 135.1 (d), 132.1 (d), 131.3 (d), 130.1 (d), 128.1 (d), 127.7 (d), 127.2 (d), 127.1 (d), 126.2 (d), 125.5 (d), 125.4 (s), 115.2 (t), 18.3 (q); MS *m/z* (%, fragment): 170 (5, M^+), 128 (100);

trans,trans-**1a**: R_f 0.75 (petroleum ether); colourless oil; UV (EtOH) λ_{max} (log ε) 275 (4.19); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.40-7.35 (m, 2H), 7.15-7.10 (m, 2H), 6.95 (dd, 1H, *J* = 17.3; 11.1 Hz), 6.65 (d, 1H, *J* = 15.5 Hz), 6.50 (dd, 1H, *J* = 15.5; 9.8 Hz), 6.19-6.15 (m, 1H), 5.81-5.74 (m, 1H), 5.55 (dd, 1H, *J* = 17.4; 1.4 Hz), 5.25 (dd, 1H, *J* = 11.1; 1.4 Hz), 1.75 (dd, 3H, *J* = 6.8; 1.4 Hz); too small a quantity of the isolated isomer for the assignment of the ^{13}C nuclei, as both geometrical isomers have the same R_f value; MS *m/z* (%, fragment): 170 (100, M^+), 127 (20).

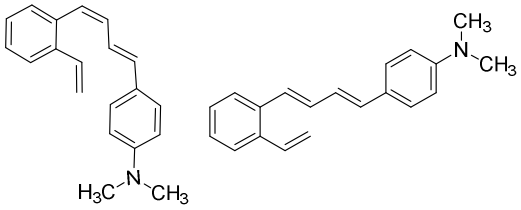


cis,trans-**2a** *trans,trans*-**2a**

1-ethenyl-2-(4-phenylbuta-1,3-dien-1-yl)benzene (2a): Yield 77.0%, lit.[19] 92.0%; according to ^{1}H NMR spectroscopy, a mixture of 53% *cis,trans*- and 47% of *trans,trans*-isomer. HRMS for $C_{18}H_{16}$: M^+_{calcd} 232.1334; M^+_{found} 232.1323 (for a mixture of isomers of **2a**).

cis,trans-**2a**: R_f 0.52 (petroleum ether); colourless oil; UV (EtOH) λ_{max} (log ε) 306 (4.46, sh), 236 (4.14, sh); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.57 (d, 1H, *J* = 7.3 Hz), 7.31-7.34 (m, 7H), 7.20 (t, 1H, *J* = 7.3 Hz), 7.03 (dd, 1H, *J* = 15.6; 11.3 Hz), 6.91 (dd, 1H, *J* = 17.5; 11.2 Hz), 6.69 (d, 1H, *J* = 15.6 Hz), 6.62 (d, 1H, *J* = 11.2 Hz), 6.50 (t, 1H, *J* = 11.2 Hz), 5.70 (dd, 1H, *J* = 17.5; 1.2 Hz), 5.29 (dd, 1H, *J* = 11.2; 1.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 137.33 (s), 136.53 (s), 135.74 (s), 135.18 (d), 134.49 (d), 131.23 (d), 130.26 (d), 129.34 (d), 128.60 (d), 127.68 (d), 127.53 (d), 127.40 (d), 126.59 (d), 125.76 (d), 125.54 (d), 115.63 (t); MS *m/z* (%, fragment): 232 (2, M^+), 128 (100);

trans,trans-**2a**: R_f 0.48 (petroleum ether); colourless crystals; mp 91-92 ºC; UV (EtOH) λ_{max} (log ε) 354 (4.33, sh), 336 (4.58), 262 (4.09) 234 (4.09); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.51 (d, 1H, *J* = 7.5 Hz), 7.41-7.45 (m, 3H), 7.31 (t, 1H, *J* = 7.5 Hz), 7.19-7.26 (m, 3H), 7.06 (dd, 1H, *J* = 17.4; 11.0 Hz), 6.97 (dd, 1H, *J* = 15.8; 10.5 Hz), 6.95 (d, 1H, *J* = 15.4 Hz), 6.83 (dd, *J* = 1H, 15.4; 10.5 Hz), 6.65 (d, 1H, *J* = 15.8 Hz), 5.62 (dd, 1H, *J* = 17.4; 1.2 Hz), 5.35 (dd, 1H, *J* = 11.0; 1.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 136.91 (s), 135.90 (s), 134.93 (s), 134.52 (d), 132.58 (d), 130.94 (d), 129.82 (d), 129.03 (d), 128.33 (d), 127.38 (d), 127.18 (d), 126.27 (d), 126.00 (d), 125.99 (d), 125.46 (d), 116.11 (t); MS *m/z* (%, fragment): 232 (100, M^+).

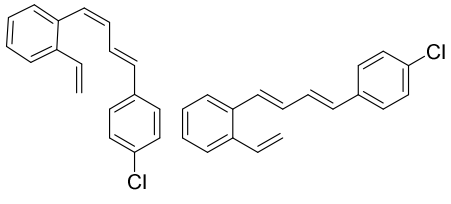


cis,trans-**3a** *trans,trans*-**3a**

4-(4-(2-ethenylphenyl)buta-1,3-dien-1-yl)-*N*,*N*-dimethylaniline (3a): Yield 63.0%, according to ^{1}H NMR spectroscopy, a mixture of 51% *cis,trans*- and 49% of *trans,trans*-isomer. HRMS for $C_{18}H_{21}N$: M^{+}_{calcd} 275.1722; M^{+}_{found} 275.1713 (for a mixture of isomers of **3a**).

cis,trans-**3a**: R_f 0.60 (petroleum ether/dichloromethane (30%)); yellow oil; UV (EtOH) λ_{max} (logε) 355 (4.16); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.50 (m, 1H), 7.27 (d, 1H, *J* = 7.2 Hz), 7.21-7.15 (m, 3H), 7.12 (dt, 1H, *J* = 7.8; 1.3 Hz), 6.86 (dd, 1H, *J* = 17.6; 11.3 Hz), 6.82-6.79 (m, 1H), 6.55 (d, 2H, *J* = 9.7 Hz), 6.53 (d, 1H, *J* = 15.9 Hz), 6.39 (t, 1H, *J* = 11.4 Hz), 6.37 (d, 1H, *J* = 11.4 Hz), 5.55 (dd, 1H, *J* = 17.4; 1.2 Hz), 5.20 (dd, 1H, *J* = 11.1; 1.2 Hz), 2.87 (s, 6H); too small a quantity of the isolated isomer for the assignment of the ^{13}C nuclei, as both geometrical isomers have the same R_f value and due to the fast isomerization of the *cis,trans*-**3** to *trans,trans*-**3a**; MS *m/z* (%, fragment): 128 (100);

trans,trans-**3a**: R_f 0.60 (petroleum ether/dichloromethane (30%)); yellow oil; UV (EtOH) λ_{max} (logε) 378 (4.33), 266 (4.09); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.54 (d, 1H, *J* = 7.8 Hz), 7.47 (d, 1H, *J* = 7.1 Hz), 7.31 (d, 2H, *J* = 9.0 Hz), 7.27 (dt, 1H, *J* = 7.7; 1.2 Hz), 7.19 (dt, 1H, *J* = 7.7; 1.2 Hz), 7.11 (dd, 1H, *J* = 17.2; 11.2 Hz), 6.91-6.81 (m, 3H), 6.71 (d, 2H, *J* = 9.0 Hz), 6.64 (d, 1H, *J* = 14.8 Hz), 5.65 (dd, 1H, *J* = 17.6; 1.5 Hz), 5.37 (d, 1H, *J* = 10.9; 1.5 Hz), 2.99 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 150.1 (s), 136.0 (s), 135.9 (s), 135.2 (d), 133.5 (d), 132.2 (d), 127.8 (s), 127.6 (2d), 127.1 (d), 126.6 (d), 125.8 (s), 125.7 (d), 125.4 (d), 116.2 (t), 112.4 (2d), 40.4 (2q); MS *m/z* (%, fragment): 275 (100, M^{+}), 134 (50).

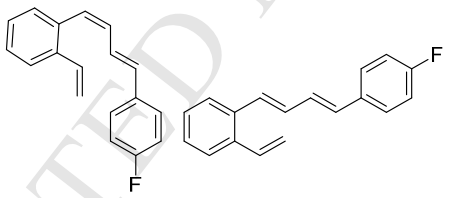


cis,trans-**4a** *trans,trans*-**4a**

1-(4-(4-chlorophenyl)buta-1,3-dien-1-yl)-2-ethenylbenzene (4a): Yield 70.0%, lit.[17] 78.0%; according to ^{1}H NMR spectroscopy, a mixture of 50% *cis,trans*- and 50% of *trans,trans*-isomer. HRMS for $C_{18}H_{15}Cl$: M^{+}_{calcd} 266.0857; M^{+}_{found} 266.0867 (for a mixture of isomers of **4a**).

cis,*trans*-**4a**: 45%; R_f 0.69 (petroleum ether/dichloromethane = 9:1); colourless oil; UV (EtOH) λ_{max} (log ε) 317 (4.43), 237 (4.33); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.56 (dd, 1H, *J* = 8.0; 2.3 Hz), 7.30 – 7.28 (m, 3H), 7.26–7.23 (m, 4H), 6.97 (dd, 1H, *J* = 15.4; 11.0 Hz), 6.90 (dd, 1H, *J* = 17.5; 11.1 Hz), 6.64 (d, 1H, *J* = 11.2 Hz), 6.61 (d, 1H, *J* = 15.4 Hz,), 6.47 (t, 1H, *J* =11.2 Hz), 5.69 (d, 1H, *J* = 17.5 Hz); 5.29 (d, 1H, *J* = 11.1 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 136.5 (s), 135.8 (2s), 135.6 (s), 135.1 (d), 133.0 (d), 130.9 (d), 130.2 (d), 129.9 (d), 128.7 (2d), 127.7 (2d), 127.6 (d), 127.4 (d), 126.1 (d), 125.8 (d), 115.7 (t); MS *m/z* (%, fragment): 266 (5, M^+), 128 (100);

trans,*trans*-**4a**: 33%; R_f 0.66 (petroleum ether/dichloromethane = 9 : 1); colourless crystals; mp 110–113 °C; UV (EtOH) λ_{max} (log ε) 340 (4.57), 329 (4.56, sh), 265 (4.53); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.51 (dd, 1H, *J* = 7.3; 1.7 Hz), 7.45 (dd, 1H, *J* = 7.3; 1.7 Hz), 7.36 (d, 2H, *J* = 8.5 Hz), 7.29 (d, 2H, *J* = 8.5 Hz), 7.27 – 7.23 (m, 2H), 7.06 (dd, 1H, *J* = 17.3; 11.0 Hz), 6.98 (d, 1H, *J* = 15.3 Hz), 6.95 (dd, 1H, *J* = 15.4; 10.5 Hz), 6.82 (dd, 1H, *J* = 15.4; 10.5 Hz), 6.61 (d, 1H, *J* = 15.4 Hz), 5.63 (dd, 1H, *J* = 17.3; 1.2 Hz), 5.36 (dd, 1H, *J* = 11.0; 1.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 135.9 (s), 135.4 (s), 134.7 (s), 134.4 (d), 132.7 (s), 131.0 (d), 130.5 (d), 130.4 (d), 129.6 (d), 128.3 (2d) 127.3 (d), 127.2 (d), 127.0 (2d), 126.3 (d), 125.4 (d), 116.1 (t); MS *m/z* (%, fragment): 266 (100, M^+), 121 (40).

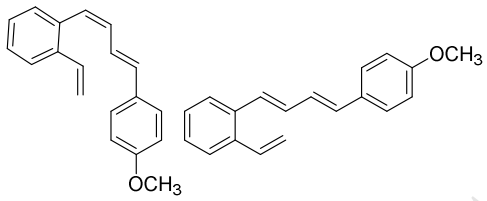


cis,trans-**5a** *trans,trans*-**5a**

1-ethenyl-2-(4-(4-fluorophenyl)buta-1,3-dien-1-yl)benzene (5a): Yield 50.0%, according to ^{1}H NMR spectroscopy, a mixture of 48% *cis*,*trans*- and 52% of *trans*,*trans*-isomer. HRMS for $C_{18}H_{15}F$: M^+_{calcd} 250.1265; M^+_{found} 250.1256 (for a mixture of isomers of **5a**).

cis,*trans*-**5a**: R_f 0.59 (petroleum ether); bright yellow oil; UV (EtOH) λ_{max} (logε) 319 (4.41), 224 (4.30); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.40-7.35 (m, 3H), 7.31-7.28 (m, 2H), 7.06 (dd, 1H, *J* = 17.2; 10.9 Hz), 6.93-6.86 (m, 3H), 6.83 (dd, 1H, *J* = 15.7; 11.2 Hz), 6.65 (d, 1H, *J* = 10.6 Hz), 6.62 (d, 1H, *J* = 15.7 Hz), 6.61 (d, 1H, *J* = 15.6 Hz), 6.48 (t, 1H, *J* = 11.2 Hz), 5.63 (dd, 1H, *J* = 17.2; 1.3 Hz), 5.29 (dd, 1H, *J* = 10.9; 1.3 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 136.3 (s), 135.7 (s), 135.4 (s), 135.2 (s), 134.8 (d), 133.1 (d), 131.6 (d), 130.9 (d), 130.6 (d), 130.2 (d), 129.6 (d), 127.9 (2d), 127.8 (2d), 124.4 (d), 125.7 (d), 115.4 (t); MS *m/z* (%, fragment): 250 (2, M^+), 128 (100);

trans,trans-**5a**: R_f 0.59 (petroleum ether); bright yellow oil; UV (EtOH) λ_{max} (logε) 343 (4.54), 269 (4.56); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.59-7.51 (m, 2H), 7.46 (dd, 1H, *J* = 7.2; 1.7 Hz), 7.27-7.15 (m, 6H), 7.01-6.94 (m, 2H), 6.62 (d, 1H, *J* = 15.6 Hz), 6.61 (d, 1H, *J* = 15.6 Hz), 5.69 (dd, 1H, *J* = 17.4; 1.3 Hz), 5.37 (dd, 1H, *J* = 11.4; 1.3 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 136.4 (s), 135.9 (s), 135.6 (s), 135.2 (s), 135.1 (d), 133.3 (d), 131.7 (d), 131.1 (d), 130.7 (d), 130.2 (d), 129.6 (d), 128.0 (2d), 127.8 (2d), 127.5 (d), 125.8 (d), 115.6 (t); MS *m/z* (%, fragment): 250 (100, M^+), 135 (90).

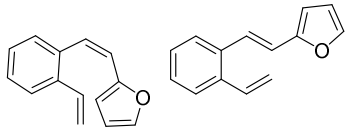


cis,trans-**6a** *trans,trans*-**6a**

1-ethenyl-2-(4-(4-methoxyphenyl)buta-1,3-dien-1-yl)benzene (6a): Yield 65.0%, lit.[18] 69.0%; according to ^{1}H NMR spectroscopy, a mixture of 50% *cis,trans*- and 50% of *trans,trans*-isomer. HRMS for $C_{19}H_{18}O$: $M^+_{calcd.}$ 262.1352; M^+_{found} 262.1347 (for a mixture of isomers **6a**).

cis,trans-**6a**: 32%; R_f 0.28 (petroleum ether/dichloromethane = 8:2); colourless oil; UV (96% EtOH) λ_{max} (log ε) 323 (4.73), 235 (4.56); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.56 (d, 1H, *J* = 9.0 Hz), 7.31 (d, 1H, *J* = 8.9 Hz), 7.28 (d, 2H, *J* = 8.7 Hz), 7.25–7.29 (m, 2H), 6.92 (dd, 1H, *J* = 17.4; 11.0 Hz), 6.90 (dd, 1H, *J* = 15.6; 11.1 Hz), 6.82 (d, 2H, *J* = 8.7 Hz), 6.63 (d, 1H, *J* = 15.6 Hz), 6.55 (d, 1H, *J* = 11.2 Hz), 4.46 (t, 1H, *J* = 11.1 Hz), 5.68 (dd, 1H, *J* = 17.4; 1.1 Hz), 5.28 (dd, 1H, *J* = 11.0; 1.1 Hz), 3.79 (s, 3H, -OCH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 158.9 (s), 136.0 (s), 135.4 (s), 134.7 (d), 133.6 (d), 130.9 (d), 129.7 (d), 129.6 (s), 127.6 (d), 127.5 (d), 127.3 (2d), 126.8 (2d), 125.2 (d), 123.0 (d), 115.0 (t), 113.6 (d), 54.8 (q); MS *m/z* (%, fragment): 262 (2, M^+), 128 (100);

trans,trans-**6a**: 37%; R_f 0.25 (petroleum ether/dichloromethane = 8:2); colourless crystals; mp 114-116 °C; UV (96% EtOH) λ_{max} (log ε) 344 (4.32); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.51 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.24 (dt, *J* = 7.5; 0.9 Hz, 1H), 7.21 (dt, *J* = 7.5; 0.9 Hz, 1H), 7.07 (dd, *J* = 17.4; 11.0 Hz, 1H), 6.91 (d, *J* = 14.7 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.80 – 6.88 (m, 2H), 6.63 (d, *J* = 14.7 Hz, 1H), 5.62 (dd, *J* = 17.4; 1.1 Hz, 1H), 5.35 (dd, *J* = 11.0; 1.1 Hz, 1H), 3.82 (s, 3H, -OCH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 158.9 (s), 135.7 (s), 135.1 (s), 134.5 (d), 132.1 (d), 131.2 (d), 129.7 (s), 128.6 (d), 127.3 (d), 127.1 (2d), 127.0 (d), 126.9 (2d), 126.2 (d), 125.3 (d), 115.9 (t), 113.7 (d), 54.8 (q); MS *m/z* (%, fragment): 262 (100, M^+).



cis-**7a** *trans*-**7a**

2-(2-(2-ethenylphenyl)ethenyl]furan (7a): Yield 71.0%, lit.[48] 85.0%; according to ^{1}H NMR spectroscopy, a mixture of 30% *cis*- and 70% of *trans*-isomer. HRMS for $C_{14}H_{12}O$: M^{+}_{calcd} 196.0957; M^{+}_{found} 196.0969 (for a mixture of isomers of **7a**).

cis-**7a**: R_f 0.50 (petroleum ether); colourless oil; UV (EtOH) λ_{max} (logε) 305 (3.96), 280 (3.99), 255 (4.13); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.60-7.10 (m, 5H), 6.89 (dd, 1H, *J* = 17.5; 10.9 Hz), 6.54 (d, 1H, *J* = 12.2 Hz), 6.50 (d, 1H, *J* = 12.2 Hz), 6.21 (dd, 1H, *J* = 3.4; 2.0 Hz), 5.90 (dd, 1H, *J* = 3.4; 0.5 Hz), 5.61 (dd, 1H, *J* = 17.5; 1.4 Hz), 5.22 (dd, 1H, *J* = 10.9; 1.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 152.1 (s), 141.5 (s), 136.4 (s), 135.9 (s), 134.9 (d), 129.2 (d), 127.6 (d), 126.7 (d), 125.3 (d), 119.8 (d), 118.2 (d), 115.2 (t), 111.2 (d), 109.5 (d); MS *m/z* (%, fragment): 196 (100, M^{+});

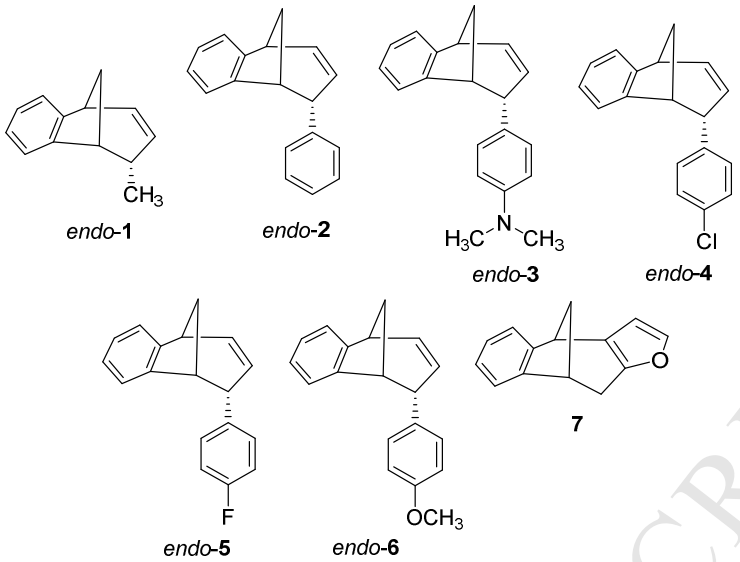
trans-**7a**: R_f 0.40 (petroleum ether); colourless oil; UV (EtOH) λ_{max} (logε) 340 (4.00), 322 (4.29), 310 (4.30), 256 (4.15); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.60-7.12 (m, 6H), 7.10 (dd, 1H, *J* = 17.5; 10.9 Hz), 6.76 (d, 1H, *J* = 16.1 Hz), 6.41 (dd, 1H, *J* = 3.4; 2.0 Hz), 6.33 (dd, 1H, *J* = 3.4; 0.5 Hz), 5.63 (dd, 1H, *J* = 17.5; 1.4 Hz), 5.35 (dd, 1H, *J* = 10.9; 1.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 153.4 (s), 142.2 (s), 136.5 (s), 135.2 (s), 135.0 (d), 127.8 (d), 127.6 (d), 126.7 (d), 125.8 (d), 124.8 (d), 118.6 (d), 116.5 (t), 111.6 (d), 108.6 (d); MS *m/z* (%, fragment): 196 (100, M^{+});

General procedure for synthesis of benzobicyclo[3.2.1]octadiene structures 1-7 by batch photoreaction: A mixture of isomers of the corresponding starting compounds **1a**-**7a** (50 mg) were dissolved in toluene (50 mL) and transferred to a quartz or pyrex vessel, purged with argon for 20 minutes, and irradiated with 16 UV lamps at 300 or 350 nm for 5 or 16 h. After removal of the solvent, GC-MS and NMR measurements showed unreacted starting material and the photoproduct **1**-**7**. The crude product was purified by column chromatography using petroleum ether/diethylether (0-50%) as eluent. In the first fractions the starting compounds **1a**-**7a** were isolated according to NMR analyses followed by the photoproducts **1**-**7**. High-molecular-weight products remained on the column.

General procedure for synthesis of benzobicyclo[3.2.1]octadiene structures 1-7 by continuous flow photoreaction: a) A 2 mL of 0.093 mmol/mL solution in toluene of mixture of isomers of

starting compound, obtained by Wittig reaction as the starting substrate for the synthesis of photoproducts **1, 2** and **4-7,** were purged with argon for 5 minutes, placed in injection loop and passed through a 19 m reactor system consisting of fluorinated ethylene–propylene copolymer (FEP) tubing (IDEX Health and Science, natural color, 1.57 mm outer diameter, 0.76 mm inner diameter), wraped around the pyrex cuvettes and placed in a Rayonet reactor, using plunger pump (piston pump; Flash Master Personal Argonaut). Reaction loop was irradiated with 16 UV lamps at 300 or 350 nm. Residence times were 6 or 12 mim, and after the removal of the solvent, full conversion to photoproducts **1, 2** and **4-7** was detected by GC-MS system and ^{1}H NMR spectra also show no unreacted starting material. Solvent was removed and crude product was purified by column chromatography using petroleum ether/diethylether (0-10%) as eluent to afford the products in 48-95% of the desired benzobicyclo[3.2.1]-derivatives **1**, **2** and **4-7** as white crystals (**1**, **5** and **7**), or as colourless oil (**2**, **4** and **6**). High-molecular-weight products remained on the column.

b) A 2 mL of 0.093 mmol/mL solution in toluene of mixture of isomers of starting compound, obtained by Wittig reaction as the starting substrate for the synthesis of dimethylamino derivative **3**, was purged with argon for 5 minutes, placed in injection loop and pumped through a 19 m reactor system consisting of fluorinated ethylene–propylene copolymer (FEP) tubing (IDEX Health and Science, natural color, 1.57 mm outer diameter, 0.76 mm inner diameter). Reaction loop was irradiated with 16 UV lamps at 350 nm. Residence time was 12 min, 60% conversion was observed by GC-MS system and NMR measurements. Solvent was removed and crude product was obtained as dark yellow oil that was purified by column chromatography using petroleum ether/diethylether (0-50%) as eluent. In the first fractions 20% of the mixture of the starting isomerrs **3a** was isolated according to NMR analyses followed by the photoproduct *endo*-**3**. High-molecular-weight products remained on the column.



11-methyltricyclo[6.3.1.0^{2,7}]dodeca-2,4,6,9-tetraene (*endo*-1): Yield 48.0%; High-molecular-weight products remained on the column. HRMS for $C_{13}H_{14}$: M^+_{calcd} 170.1157; M^+_{found} 170.1148.

endo-**1**: R_f 0.60 (petroleum ether); colourless crystals; mp 49 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.21-6.92 (m, 4H), 6.14 (m, 1H), 5.03 (m, 1H), 3.15 (m, 2H), 2.64 (m, 1H), 2.41 (m, 1H), 2.18 (d, 1H, J = 9.2 Hz), 0.82 (d, J = 10.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 143.3 (s), 142.1 (s), 125.9 (d), 125.8 (d), 125.3 (d), 125.2 (d), 123.3 (d), 120.1 (d), 42.5 (t), 39.4 (d), 37.5 (d), 29.2 (d), 10.8 (q); MS *m/z* (%, fragment): 170 (100, M^+), 115 (20).

11-phenyltricyclo[6.3.1.0^{2,7}]dodeca-2,4,6,9-tetraene (*endo*-2): Yield 95.0%, lit.[19] 90.0%; High-molecular-weight products remained on the column. HRMS for $C_{18}H_{16}$: M^+_{calcd} 232.1334; M^+_{found} 232.1341.

endo-**2**: R_f 0.44 (petroleum ether); colourless crystals; mp 51 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.17-7.18 (m, 3H), 7.12 (d, 1H, J = 7.3 Hz), 7.03 (t, 1H, J = 7.4 Hz), 6.81 (t, 1H, J = 7.4 Hz), 6.73-6.76 (m, 2H), 6.37 (ddd, 1H, J = 9.5 Hz; J = 6.0 Hz; J = 2.5 Hz), 6.18 (d, 1H, J = 7.3 Hz), 5.33 (dt, 1H, J = 9.5 Hz; J = 2.5 Hz), 3.98 (m, 1H), 3.38 (t, 1H, J = 4.7 Hz), 3.29 (dd, 1H, J = 6.0; 4.7 Hz), 2.52 (dt, 1H, J = 9.9; 4.7 Hz), 2.38 (d, 1H, J = 9.9 Hz,); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 152.27 (s), 142.44 (s), 141.93 (s), 132.71 (d), 128.21 (d), 127.60 (d), 126.34 (d), 126.10 (d), 126.05 (d), 125.97 (d), 124.89 (d), 120.03 (d), 48.59 (d), 46.29 (d), 44.13 (t), 40.37 (d); MS *m/z* (%, fragment): 232 (100, M^+), 117 (25), 115 (10).

***N*,*N*-dimethyl-4-{tricyclo[6.3.1.0^{2},^{7}]dodeca-2,4,6,10-tetraen-9-yl}aniline (*endo*-3):** Yield 24.0%; High-molecular-weight products remained on the column. HRMS for $C_{18}H_{21}N$: M^{+}_{calcd} 275.1722; M^{+}_{found} 275.1733.

endo-**3**: R_f 0.57 (petroleum ether/dichloromethane (30%)); dark yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.20-7.18 (m, 3H), 7.10 (d, 1H, *J* = 7.2 Hz), 7.05 (t, 1H, *J* = 7.2 Hz), 6.83-6.76 (m, 2H), 6.35 (dt, 1H, *J* = 9.0; 2.5 Hz), 6.20 (d, 1H, *J* = 7.3 Hz), 5.30 (m, 1H), 3.89 (ddd, 1H, *J* = 9.8; 4.7; 2.5 Hz), 3.30 (t, 1H, *J* = 4.7 Hz), 3.21 (d.d., 1H, *J* = 6.8; 4.7 Hz), 2.86 (s, 6H), 2.44 (dt, 1H, *J* = 9.9; 4.7 Hz), 2.30 (d, 1H, *J* = 9.9 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 152.6 (s), 152.4 (s), 142.1 (s), 138.3 (s), 135.4 (d), 127.9 (2d), 127.8 (2d), 126.8 (d), 125.5 (d), 125.2 (d), 124.8 (d), 121.7 (d), 53.9 (d), 49.2 (d), 46.9 (d), 46.5 (t), 45.7 (2q); MS *m/z* (EI) 275 (M^{+}, 100%), 121 (50).

11-(4-chlorophenyl)tricyclo[6.3.1.0^{2},^{7}]dodeca-2,4,6,9-tetraene (*endo*-4): Yield 83.0%, lit.[17] 77.0%; High-molecular-weight products remained on the column. HRMS (-H^{+}) for $C_{18}H_{15}Cl$: $M^{+}_{calcd.}$ 265.0789; M^{+}_{found} 265.0786.

endo-**4**: R_f 0.66 (petroleum ether/dichloromethane = 9 : 1); colourless oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.14 (d, 2H, *J* = 8.4 Hz), 7.12 (d, 1H, *J* = 7.3 Hz), 7.03 (dt, 1H, *J* = 7.4; 1.0 Hz), 6.84 (dt, 1H, *J* = 7.4; 1.0 Hz), 6.65 (d, 2H, *J* = 8.3 Hz), 6.40–6.35 (m, 1H), 6.23 (d, 1H, *J* = 7.3 Hz), 5.25 (ddd, 1H, *J* = 9.6; 4.0; 1.9 Hz), 3.96–3.92 (m, 1H), 3.34 (t, 1H, *J* = 9.4; 4.7 Hz), 3.29 (dd, 1H, *J* = 6.1; 4.7 Hz), 2.54–2.50 (m, 1H), 2.37 (d, 1H, *J* = 10.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 140.6 (s), 137.3 (s), 132.9 (s), 130.9 (s), 134.7 (d), 129.2 (2d), 127.3 (d), 125.7 (d), 125.6 (d), 125.4 (2d), 124.7 (d), 119.7 (d), 48.0 (d), 45.3 (d), 43.7 (t), 39.9 (d).

11-(4-fluorophenyl)tricyclo[6.3.1.0^{2},^{7}]dodeca-2,4,6,9-tetraene (*endo*-5): Yield 87.0%; High-molecular-weight products remained on the column. HRMS for $C_{18}H_{15}F$: M^{+}_{calcd} 250.1265; M^{+}_{found} 250.1256.

endo-**5**: R_f 0.60 (petroleum ether); colourless crystals; mp 53-54 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.11 (d, 1H, *J* = 6.9 Hz), 7.04-6.99 (m, 2H), 6.87-6.81 (m, 2H), 6.66 (m, 2H), 6.37-6.33 (m, 1H), 6.20 (d, 1H, *J* = 7.9 Hz), 5.27-5.26 (m, 1H), 3.95-3.93 (m, 1H), 3.33 (t, 1H, *J* = 4.8 Hz), 3.27 (dd, 1H, *J* = 6.4; 4.8 Hz), 2.50 (dt, 1H, *J* = 9.8; 4.7 Hz), 2.35 (d, 1H, *J* = 9.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 141.8 (s), 138.2 (s), 135.8 (s), 135.5 (s), 135.0 (d), 129.7 (2d), 129.6 (d), 126.2 (2d), 126.1 (d), 125.1 (d), 120.2 (2), 48.6 (d), 45.5 (d), 44.1 (t), 40.3 (d); MS *m/z* (%, fragment): 250 (100, M^{+}), 135 (25).

11-(4-methoxyphenyl)tricyclo[6.3.1.0^{2,7}]dodeca-2,4,6,9-tetraene (*endo*-6): Yield 70.0%, lit.[18] 55.0%; High-molecular-weight products remained on the column. HRMS for HRMS for $C_{19}H_{18}O$: $M^+_{calcd.}$ 262.1352; M^+_{found} 262.1351.

endo-**6**: R_f 0.27 (petroleum ether/dichloromethane = 8:2); colourless crystals; mp 45-47 °C; ^{1}H NMR (CDCl3, 600 MHz) δ/ppm: 7.11 (d, 1H, *J* = 7.3 Hz), 7.03 (dt, 1H, *J* = 7.3; 1.0 Hz), 6.82 (dt, 1H, *J* = 7.3; 1.0 Hz), 6.72 (d, 2H, *J* = 8.6 Hz), 6.64 (d, 2H, *J* = 8.6 Hz), 6.32-6.36 (m, 1H), 6.25 (d, 1H, *J* = 7.3 Hz), 5.28 (dt, 1H, *J* = 9.6; 2.6 Hz), 3.91-3.94 (m, 1H), 3.77 (s, 3H), 3.35 (t, 1H, *J* = 4.5 Hz), 3.27 (dd, 1H, *J* = 6.3; 4.7 Hz), 2.49-2.53 (m, 1H), 2.37 (d, 1H, *J* = 9.9 Hz); 13C NMR (CDCl3, 75 MHz) δ/ppm: 157.6 (s), 152.0 (s), 141.7 (s), 134.2 (s), 134.1 (d), 128.8 (2d), 126.3 (d), 125.8 (d), 125.5 (d), 124.5 (d), 119.6 (d), 112.6 (2d), 52.4 (q), 48.2 (d), 45.0 (d), 43.7 (t), 40.3 (d); MS *m/z* (%, fragment): 262 (100, M^+), 154 (75), 115 (50).

5-oxatetracyclo[6.6.1.0^{2,6}.0^{9,14}]pentadeca-2(6),3,9(14),10,12-pentaene (7): Yield 92.0%, lit.[16] 90.0%; High-molecular-weight products remained on the column. HRMS for $C_{14}H_{12}O$: M^+_{calcd} 196.0957; M^+_{found} 196.0950.

endo-**7**: R_f 0.41 (petroleum ether); colourless crystals; mp 58-59 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz) δ/ppm 7.30-6.90 (m, 5H), 6.30 (d, 1H, *J* = 2.0 Hz), 3.78 (d, 1H, *J* = 4.5 Hz), 3.57 (dt, 1H, *J* = 5.0; 1.0 Hz), 3.11 (dd, 1H, *J* = 16.0; 5.0 Hz), 2.58 (dd, 1H, *J* = 16.0; 1.0 Hz), 2.39 (dt, 1H, *J* = 10.0; 5.0; 4.5 Hz), 2.01 (d, 1H, *J* = 10 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 151.9 (s), 146.7 (s), 144.8 (s), 140.1 (d), 126.4 (d), 126.1 (d), 124.3 (s), 123.8 (d), 120.5 (d), 108.7 (d), 43.0 (t), 40.4 (d), 39.3 (d), 30.9 (t); MS *m/z* (EI) 196 (M^+, 100%), 167 (25).

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5. Supporting Information

Supporting information consists of actinometry experiments, mass spectra of the photoproducts **1**-**7**, table of biological targets and effects predicted by Pass (*in silico*) for structures **1**-**7** and table with general values for prediction of physico-chemical and ADME properties.

Flow-photochemical Synthesis of the Functionalized Benzobicyclo[3.2.1]octadiene Skeleton

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Highlights

- A convenient practical home-made continuous flow-photochemistry setup enables efficient intramolecular photocycloaddition.
- The first application of continuous flow methodology in the synthesis of functionalized benzobicyclo[3.2.l]-skeleton.
- Higher yields and shorter reaction times in comparison to those obtained in traditional batch photoreactor.
- Promising calculated physico-chemical and ADME properties of the obtained potentially bioactive photoproducts.

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