Visible Light-driven Metal-free C–H Functionalization: Access to New Bioactive Tetrahydroisoquinoline-Butenolide Hybrids via Domino Amine Oxidation/Vinylogous Mannich Reaction

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Abstract: An efficient metal-free visible light-driven two-step domino reaction towards new bioactive tetrahydroisoquinoline-butenolide hybrid compounds was developed for the first time. Combination of fluorescein as photosensitizer and thiourea as an additive was found to be the most effective way to promote an aerobic amine oxidation/vinylogous Mannich domino reaction sequence with yields up to 97% for a broad substrate scope. While fluorescein without thiourea additive gave product in 84% yield, it was even observed that thiourea in absence of fluorescein is also able to promote formation of product with good yield of 75%, which is explained by a potential role of thiourea as an electron-transfer mediator in light-induced amine oxidation. Both experimental and computational evidence supported the crucial role of singlet oxygen in the developed C–H functionalization reaction. In addition, *in vitro* studies of tetrahydroisoquinoline-butenolide hybrid compounds demonstrated their high antischistosomal and anti-cancer activities.

Introduction

Tetrahydroisoquinolines are ubiquitous in synthetic drugs, biologically active natural compounds and pharmaceuticals.[1] Derivatives containing a butenolide moiety at C-1, turned out to be highly active against human stomach cancer and ovarian cancer cells (Figure 1a).[2] Furthermore, a wide variety of 1-substituted derivatives of N-arylated tetrahydroisoquinolines are core structures in compounds with high pharmacological activity.[3] Moreover, tetrahydroisoquinoline-butanolides, accessible *via* hydrogenation of the butenolide moiety, act on the human central nervous system (Figure 1a).[4]

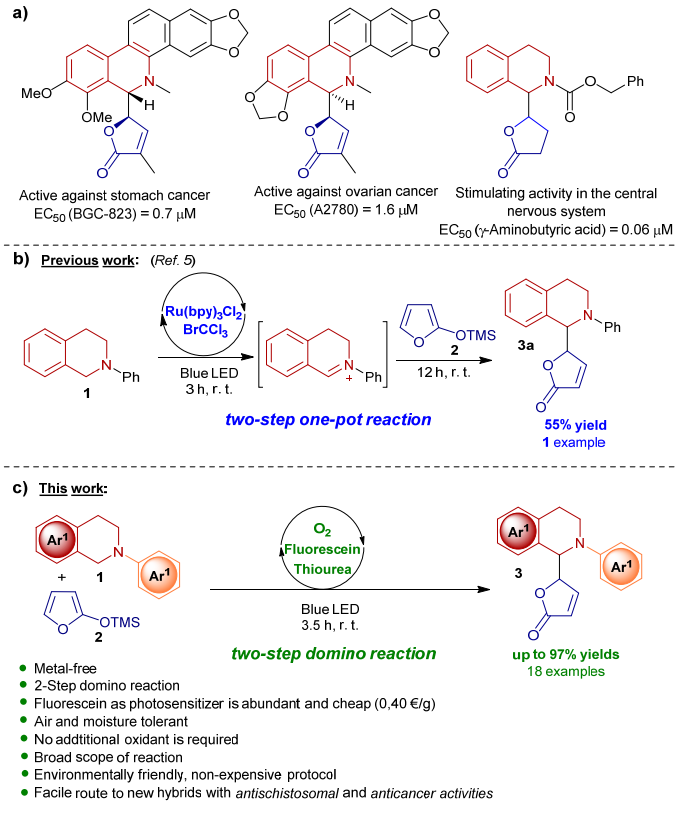


Figure 1. a) Selected examples of bioactive tetrahydroisoquinoline-butenolides[2] and tetrahydroisoquinoline-butanolide.[4] **b)** and **c)** Survey of the visible light-driven synthesis of tetrahydroisoquinoline-butenolides: *previous*[5] and *this work*.

Butanolide derivatives e.g., *γ*-butyrolactones, can be found also in many natural products and bioactive compounds.[6]

Several already existing conventional and photochemical metal-catalyzed approaches towards tetrahydroisoquinoline-butenolides underline the high demand for these structures.[7] Photochemical reactions have an especially high appeal, as visible light is an abundant, clean, and renewable reagent in chemistry. Visible light has additional advantages over UV-radiation, since side reactions are reduced and the reaction can be performed in simple glass reactors[8] and under mild conditions with high selectivity.[8-9]

Until the present, there is only a single example of photochemical synthesis of tetrahydroisoquinoline-butenolide (see compound **3a** in Figure 1b) employing a light-induced vinylogous Mannich reaction,[5] using 2-(trimethylsiloxy)furan. Therein, a ruthenium complex was used as a photosensitizer in a sequential two-step one-pot process *via* an in situ generated iminium ion to obtain the product **3a** in a moderate yield of 55% and the developed protocol was not expanded to other substrates. While ruthenium or iridium complexes are very efficient photosensitizers and/or photoredox catalysts,[10] these metals are expensive and not abundant. Furthermore, their complexes are mostly not commercially available and many of them are air- and moisture- sensitive. In contrast, organic photosensitizers are cheap, easy to handle and readily available.[11] Therefore, a metal-free photochemical synthetic route is highly desirable but has not been reported so far.

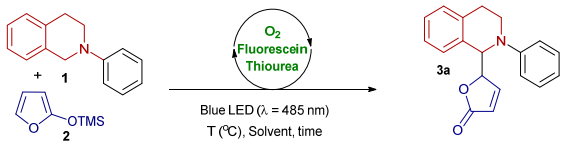
Herein, we report a first example of a metal-free visible light-induced atom economical and sustainable two-step domino process, employing an organic dye (fluorescein) as photosensitizer to obtain tetrahydroisoquinoline-butenolides with a broad scope and high yields (up to 97%, Figure 1c). Furthermore, we demonstrate the application of simple thiourea additive to significantly improve the product yield. Moreover, we disclose that the new compounds possess high antischistosomal and anticancer activities.

Results and Discussion

We initiated our study of metal-free and visible light-induced vinylogous Mannich reaction between N-phenyl tetrahydroisoquinoline **1** and 2-(trimethylsiloxy)furan **2**, using fluorescein as an organic photosensitizer (Table 1), because we envisioned the possibility of a two-step domino, rather than a sequential two-step one-pot process (Figure 1b vs. Figure 1c). To optimize the yield of C–H functionalization product **3**, several reaction parameters were varied, for instance solvent, reaction time and temperature, and influence of additives (Table 1). Notably, yield of product **3** could be increased by using polar solvents like water or alcohols (entries 3-7) in comparison to less polar solvents (entries 1-2). Water as solvent resulted in lower yields (entry 3) than alcohols, since the solubility of the substrates was diminished. Shorter reaction time (e.g. 5 hours, cf. entry 6 with entry 5) and carrying out the reaction at room temperature, instead of at elevated temperature (55 °C, entry 7) at the same reaction time, resulted even in somewhat higher yields. Addition of thiourea further improved the yield (cf. entry 6 with entry 8). Further reduction of reaction time to 3.5 hours gave the desired product in remarkably high yield of 97% (entry 9).

To evaluate impact of certain reaction components on the product yield, we systematically studied the reaction without either irradiation (entry 10), photosensitizer (entry 11), additive (entry 12), as well as without photosensitizer and additive (entry 13) and under exclusion of air (i.e. under argon, entry 14), revealing the indispensable role of irradiation and of oxygen and the crucial role of the thiourea additive. With two equivalents of thiourea (entry 15), full conversion was achieved in half the reaction time with only a small reduction in yield with respect to entry 9. When adding sodium acetate instead of thiourea additive, the reaction did not finish after 3.5 h and therefore only 67% yield was obtained (entry 16, cf. entry 9). Eventually, addition of 10 mol% NaN_3 together with thiourea significantly decreased the yield from 97% (entry 9) to 32% (entry 17).

Table 1. Optimization of the reaction conditions.



	t (h)	T (°C)	Solvent	Photo-sensitizer	Additive	Yield (%)
1	18	r. t.	Toluene	**I**	-	19
2	18	r. t.	MeCN	**I**	-	34
3	18	r. t.	H_2O	**I**	-	38
4	18	r. t.	EtOH	**I**	-	54
5	18	r. t.	MeOH	**I**	-	66
6	5	r. t.	MeOH	**I**		72
7	5	55	MeOH	**I**	-	55
8	5	r. t.	MeOH	**I**	Thiourea	86
9	3.5	r. t.	MeOH	**I**	Thiourea	**97**
10	3.5	r. t.	MeOH	**I**	Thiourea	5[a]
11	3.5	r. t.	MeOH	-	Thiourea	75
12	3.5	r. t.	MeOH	**I**	-	84
13	3.5	r. t.	MeOH	-	-	11
14	3.5	r. t.	MeOH	**I**	Thiourea	9[b]
15	1.25	r. t.	MeOH	**I**	Thiourea	88[c]
16	3.5	r. t.	MeOH	**I**	NaOAc	67
17	3.5	r. t.	MeOH	**I**	Thiourea/ NaN_3	32[d]

For all experiments, 5 mol% of photosensitizer, 20 mol% of additive and irradiation from a blue LED at 485 nm wavelength were used. [a]Experiment was carried out in darkness. [b]Experiment was carried out under Argon atmosphere. [c] 2 equiv. of thiourea were used. [d]Experiment was carried out with 10 mol% NaN_3.

Azides are known to intercept singlet oxygen.[12] Therefore, our observation of decrease in yield (entry 17) shows the involvement of singlet oxygen in the studied reaction. Singlet oxygen might form by electron transfer from unreacted excited state fluorescein,

followed by a pH-dependent disproportionation of superoxide radical anion $O_2^{-\bullet}$ to $^1O_2$.[13] Indeed, addition of NaOAc, which acts as a base in protic solvents through hydrolysis, led to yield reduction (entry 16), because the increase in pH value reduced the amount of singlet oxygen formed. Singlet oxygen has been recognized since recently as important reactive species in photosensitized oxidation reaction in solution.[14]

The supportive effect of thiourea derivatives on various photocatalysed reactions has already been reported in the literature. Notably, König and co-workers reported a thiourea-enhanced flavin photooxidation of benzyl alcohol, in which thiourea acts as a mediator in electron transfer photocatalysis with flavin as chromophore, involving highly reactive oxidised radical intermediates of thiourea and oxygen as sacrificial oxidant.[15] Recently, Jacobsen, Stephenson and co-workers reported an oxidative C–H functionalization of tetrahydroisoquinolines towards β-amino esters via combination of photoredox reaction, using a ruthenium complex as photocatalyst, and subsequent anion-binding organocatalysis, using thiourea.[16] Interestingly, very recently Kokotos employed Schreiner's thiourea as a catalyst in a photochemical synthesis of acetals without using a photosensitizer and in which oxygen is not involved.[17] These reports underline the versatility and multi-faceted role of thiourea in photochemical reactions and its role in our photocatalyzed two-step domino reaction (amine oxidation/vinylogous Mannich) is apparently not trivial.

Having observed a positive influence of thiourea on the yields (entry 9 vs. entry 12), we decided to study the reaction scope of our light-induced two-step domino reaction under the optimised conditions. We expanded, therefore, our developed synthesis towards γ-butenolide Mannich products of other tetrahydroisoquinolines **3a–3o** and tryptolines **3p–3r**. The investigation of the substrate tolerance is depicted in Figure 2. A correlation between yield of the reaction and the presence of aryl substituent of the nitrogen was observed. Electron withdrawing groups (EWG) like chlorine and bromine (**3b**, **3d, 3e** and **3f**) or weakly electron donating groups (EDG) like methyl moieties (**3h** and **3j**) gave relatively higher yield when in para- or meta-position, but relatively lower yields, when in ortho-position (**3c** and **3i**). Stronger EDGs like methoxy moieties (**3k** and **3l**) had an effect opposite to that of EWG, i.e. methoxy substituent in para-position (**3k**) lowered the yield relatively (to 52%), while the same substituent resulted in relative enhancement of the product yield (to 87%) when in ortho-position (**3l**). In general, EWG in ortho position had a yield reducing effect, while the same EWG in meta or para position increased the yield (**3c** cf. **3b**, **3d**). Methoxy substituents on the benzene ring of the tetrahydroisoquinoline facilitates crystallization of the product precipitate during the reaction and thereby increases the yield of the products (**3o** vs. **3h** and **3g** vs. **3n**). Tryptolines in general gave lower yields (see **3p-r**). Apart from this, the same trends were observed.

The obtained C–H functionalization products might be excellent starting compounds to generate tetrahydroisoquinoline-γ-butanolides, which are potentially bioactive compounds (Figure 1a).[4, 18] Since the synthesis of this compound class is highly desirable, we have chosen tetrahydroisoquinoline-butenolides **3a** and **3k** to showcase hydrogenation of the butenolide moiety using hydrogen and Pd/C towards tetrahydroisoquinoline-γ-butanolides **4a** and **4k** in 68% and 81% yield, respectively (Figure 3).

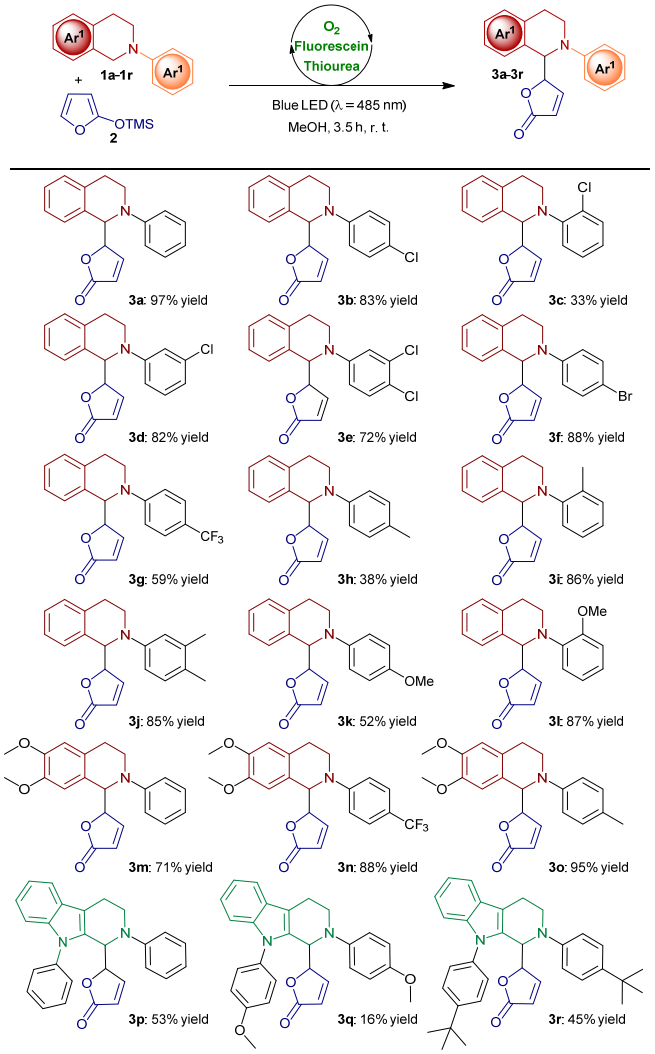


Figure 2. Scope of the metal-free visible light-driven C–H functionalization reaction.

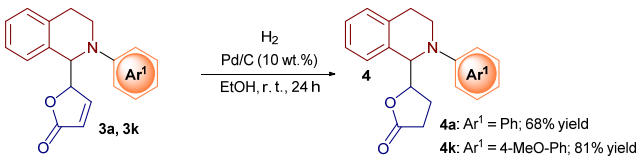


Figure 3. Synthesis of tetrahydroisoquinoline-butanolides **4a** and **4k** *via* hydrogenation of the butenolide moieties in the Mannich products **3a** and **3k**.

Next, the mechanism for visible light-induced metal-free vinylogous Mannich reaction was investigated (Figure 4), based on a reasonable model of photocatalytic C–H oxidation of cyclic tertiary amines, in which the same substrates were used and the mechanism of which was supported by DFT calculations.[19] Initially, fluorescein (**FI**) is excited by visible light (at 485 nm). Excited state fluorescein (**FI***) can undergo a single-electron transfer (**SET**) with tertiary amine **I**. As a consequence, reduced radical anion photosensitizer ($\mathbf{FI}^{-\bullet}$) and the radical cation of the amine (**II**) are generated. Through a redox reaction, an electron transfer (**ET**) between ambient molecular oxygen and reduced fluorescein ($\mathbf{FI}^{\bullet}$), superoxide radical anion ($\mathbf{O_2}^{-\bullet}$) is formed. The energy released in this redox reaction was calculated using

experimental redox potentials in water. The redox potential of fluorescein anion radical is +0.71 V and that of molecular oxygen is -0.33 V, giving an overall Gibbs free energy of -9 kcal/mol.[20]

Superoxide anion radical $\mathbf{O_2}^{-\bullet}$ can either deprotonate radical cation **II** to form α-amino radical **III** and a hydroperoxide radical followed by subsequent oxidation to give iminium ion **IV** (***Path 1***, Figure 4), or, alternatively abstract homolytically an H-atom from **II** to give iminium ion **IV** and a hydroperoxide anion directly (***Path 2***). DFT-calculations reveal that both pathways are thermodynamically feasible. Formation of iminium ion **IV** by ***Path 2*** is approximately 33.6 kcal/mol downhill. While the first step on ***Path 1***, involving formation of *α*-amino radical **II**, is exergonic by only 11.9 kcal/mol, for the second step on ***Path 1***, five different possible reactive oxygen species have been considered as reaction partners of amine radical **III** to give iminium ion **IV** in five different reactions (**a**-**e**) in a second step: **IV** can conceivably generated from **III** by reaction with a hydroperoxide radical (**a,** ΔG = -21.7 kcal/mol), triplet oxygen (**b**, ΔG = -6.7 kcal/mol)**,** singlet oxygen (**c**, ΔG = -29.2 kcal/mol), superoxide radical anion (**d**, ΔG = 19.5 kcal/mol) or with excited state fluorescein **Fl*** (**e**, ΔG = -55.1 kcal/mol). The path **d** is endergonic and is therefore precluded. The most favourable process is the path **e**, while **c** is the second most favourable reaction. This might explain why the whole process is still possible even in absence of fluorescein (entries 11 and 13). At the final stage of this cascade, the iminium ion **IV** can be attacked by (trimethylsiloxy)furan **VII** to give desired Mannich product **VIII**.

Based on DFT calculations, thiourea **V** does not appear to interact with either the superoxide and OOH radical in an exergonic process (see the SI). Conversion of the amine radical cation **II** to the amine radical **III** by deprotonation with thiourea is also an uphill process (ΔG = 6.5 kcal/mol), as well as the formation of the iminium ion **IV** from amine radical cation **III** by H atom transfer to thiourea **V** (ΔG = 28 kcal/mol). In contrast to this, nucleophilic attack by thiourea's sulphur atom on the iminium ion **IV** (Figure 4) was found to be an exothermic process (ΔH = -7.8 kcal/mol), even though inclusion of entropic factors renders this bimolecular process about 3 kcal/mol endergonic. Since the accurate description of entropic penalty in solvation computation is challenging, the free energy calculations in this case should be treated as semi-quantitative. Hence, it remains unclear whether the adduct **VI** plays a significant role in the whole reaction network.

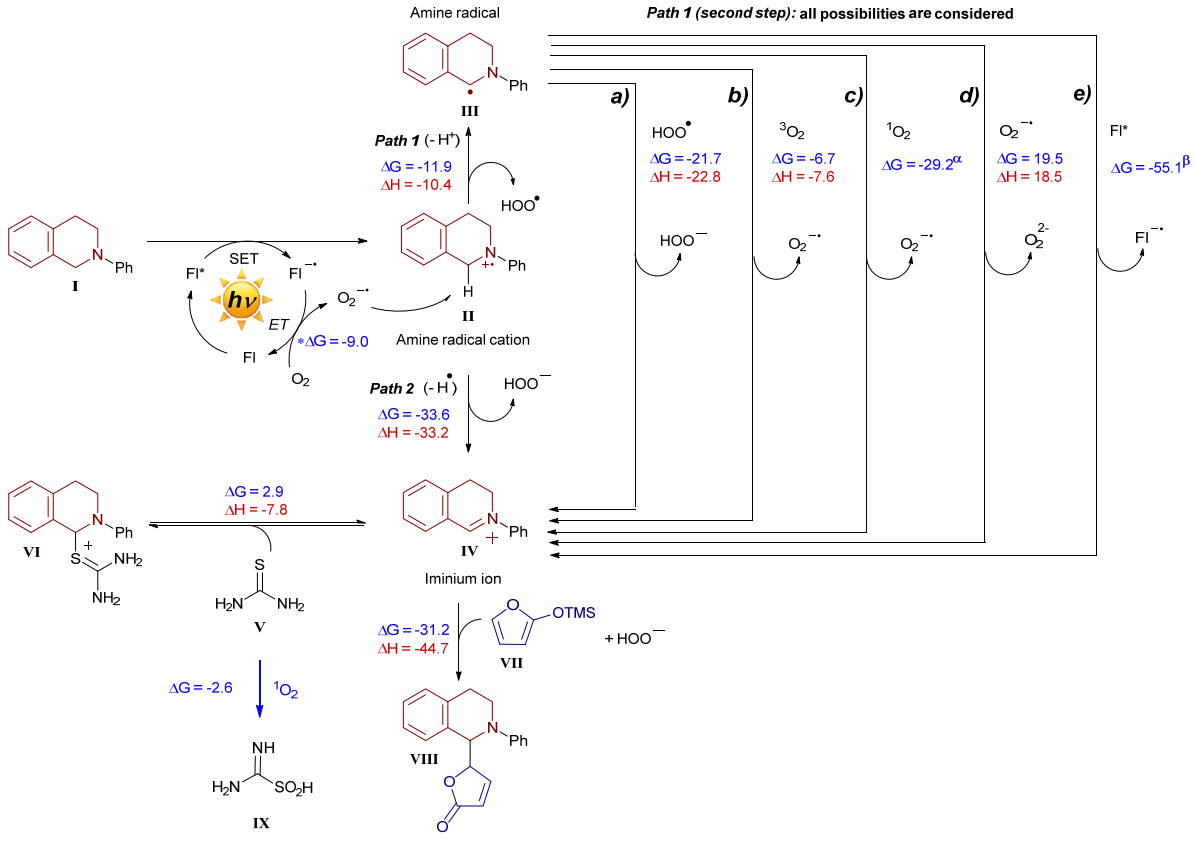


Figure 4. Mechanism of the metal-free light-induced vinylogous Mannich reaction and calculated energies of the reaction steps (energies in kcal/mol, UM06-2X(D3)/6-311++G(d,p), Int = UF, solvent = methanol) in presence of fluorescein. *Calculated using redox potentials in H_2O. **α**: Gibb's free energy for reaction with singlet O_2 was calculated using the Gibb's free energy for triplet O_2 plus 22.5 kcal/mol.[21] **β**: see SI. Thiourea might act as a singlet oxygen trap (**V** -> **IX**) in the photocatalytic vinylogous Mannich reaction of N-arylated 1,2,3,4-isothiocyanates and therefore possibly diminishes photobleaching of photosensitizer.[22]

A possible role of thiourea is intercepting the reactive hydroxy radicals. This is a favourable reaction (ΔG = -4.2 kcal/mol, see SI) which would help protect the intermediates from overoxidation towards δ-lactones and thereby improve overall yield of **VIII**.[19] As the direct formation of singlet molecular oxygen during the photochemical process using fluorescein is known too,[23] thiourea might also possibly diminish the extent of photobleaching of fluorescein by scavenging the

excess singlet oxygen. Such process is nearly thermoneutral (ΔG = 2.6 kcal/mol) and can lead to the known oxidative formation of compound **IX**.[22] At this point, we do not know yet whether the singlet oxygen, which is obviously (according to entry 17 in Table 1) involved in the generation of **IV** (Figure 4), is formed directly by energy transfer from excited fluorescein, or is produced as a result of electron transfer and subsequent disproportionation of the superoxide radical anion.

Experimentally however (entry 13), we found that irradiation alone is already sufficient to generate 11% yield of product **VIII**. This could be explained either by a certain photosensitivity of the tetrahydroisoquinoline **I** itself, or alternatively, but less likely, by a certain amount of singlet oxygen formed from triplet oxygen even in absence of a sensitizer. At any rate, this result is at least evidence that singlet oxygen alone (i.e. with or without additional formation of superoxide radical anion) must apparently also be able to bring about the sequence of oxidation steps (**I** -> **II**, **II** -> **IV** and **III** -> **IV**). Moreover, when adding thiourea (entry 11), we observed a dramatic increase in product yield to 75%, even though the photosensitizer fluorescein is absent! As thiourea itself is not known as a photosensitizer, the only conceivable explanation is that thiourea here acts as a sort of mediator (similar to the system reported by König.[15]) for a different sensitizer already present in the system, namely either reactant tetrahydroisoquinoline **I** or spontaneously formed iminium ion **IV** or even product **VIII**.

Hence, in light of these experimental findings, there must obviously exist here two, apparently additive, photochemical routes towards **VIII**: one in which fluorescein is assisting by producing the amine radical cation and either superoxide anions and singlet oxygen (or both) to give **IV** via ***Path 1*** or ***Path 2*** (with ***Path 1*** thermodynamically favoured), and a second one, in which thiourea assists in conjunction with the available N-heterocycles to give also singlet oxygen, which then further reacts to generate iminium ion **IV** via ***Path 1*** alone. This could explain why we observe the highest product yield, when both fluorescein and thiourea are present together in the reaction mixture (entry 9). Assuming thiourea's role as a mere scavenger of excess singlet oxygen, as mentioned above, is not in accord with all the experimental facts observed.

Antischistosomal activities

Given that the compounds contain a tetrahydroisoquinoline subunit similar to praziquantel, the standard treatment of schistosomiasis,[24] four compounds were tested against *Schistosoma mansoni*. In a first step, compounds were tested against newly transformed schistosomula (NTS) (Table 2). All compounds showed high activity at concentrations at 10 µM, with **3a** and **3j** killing all worms. EC_{50} values were similar (**3e**, **3k**) or even lower (**3a**, **3j**) than the one of praziquantel (2.2 µM). In a next step, compounds were tested on adult worms. Good activity was observed with compound **3e**, with an EC_{50} value of 1.44 µM.

Table 2. Efficacy test of compounds **3a**, **3e**, **3j** and **3k** against NTS and adult *S. mansoni*.

Compound	NTS			Adult S. mansoni		
	Effect in % 10 µM ± SD	Effect in % 1 µM ± SD	EC_{50} value (µM)	Effect in % 10 µM ± SD	Effect in % 1 µM ± SD	EC_{50} value (µM)
3a	100.0 ± 0.0	18.0 ± 2.0	1.51	24.5 ± 0.02	ND	ND
3e	75.0 ± 0.0	33.9 ± 1.8	2.38	64.7 ± 8.0	47.1 ± 4.0	1.44
3j	100.0 ± 0.0	35.7 ± 0.0	1.1	47.1 ± 4.0	ND	ND
3k	68.8 ± 6.3	35.7 ± 3.6	2.67	33.3 ± 4.0	ND	ND
Praziquantel	-	-	2.2[a]	-	-	0.1[a]

SD: standard deviation; [a]EC_{50} value was previously reported[25]

Anticancer activities

The cytotoxicity study (MTT assay), has been performed to analyze the half maximal inhibitory concentration (EC_{50}) of chemically synthesized hybrids. For the study, five contrasting human cancer cell lines named DU145, SKOV3, MCF7, A549, HELA along with one normal human cell line i.e. HEK 293 were used.[26] All the studied hybrids (**3a**, **3e**, **3j**, **3k**) when compared to that of approved drugs (Doxorubicin and Etoposide) showed *high anti-cancer potency*, comparable to the standards. From Table 3 it is clear, that all the hybrids were inhibiting cancer cells without harming the normal cells, indicated by the specificity of tested compounds to cancer cells. Since the test compounds bear a *α*,*β*-unsaturated ketone moiety in their molecular framework, most likely the compounds might be acting as NF κ-B inhibitors, as targeting of such Michael acceptors on nuclear transcription factors is well established.[27]

Table 3 EC_{50} (half maximal inhibitory concentration) and CC_{50} after 24 hour of drug treatment; DU 145 (human prostate cancer), SKOV3 (human ovarian cancer), MCF-7 (human breast cancer), A549 (human lung cancer), HELA (human cervical cancer) and HEK 293 (human embryonic kidney cell line). ± SD, standard deviation of experiment performed in triplicates.

Compounds	EC_{50} DU145 [µM]	EC_{50} SKOV3 [µM]	EC_{50} MCF-7 [µM]	EC_{50} A549 [µM]	EC_{50} HELA [µM]	CC_{50} HEK 293 [µM]
3a	8.58 ± 1.62	8.18 ± 1.13	8.20 ± 0.68	11.20 ± 0.84	7.64 ± 0.76	>100
3e	9.47 ± 1.57	9.81 ± 0.38	9.86 ± 0.96	9.82 ± 0.92	11.17 ± 0.13	>100
3j	8.92 ± 0.60	10.58 ± 0.45	8.81 ± 1.50	10.16 ± 0.95	11.49 ± 0.45	>100
3k	11.16 ± 0.92	10.35 ± 2.08	8.17 ± 0.24	8.26 ± 0.72	9.99 ± 1.13	>100
Doxorubicin	4.79 ± 0.59	3.14 ± 1.23	4.53 ± 1.77	5.55 ± 1.00	8.01 ± 0.54	>100
Etoposide	9.83 ± 1.70	4.73 ± 1.56	7.45 ± 0.27	8.13 ± 1.53	7.30 ± 0.83	>100

Conclusion

In summary, we developed a facile visible light-driven metal-free two-step domino reaction (amine oxidation/vinylogous Mannich), which allows a straightforward, waste reducing and cost-effective access to a broad scope of new tetrahydroisoquinoline-butenolide and tryptoline-butenolide hybrid compounds with yields up to 97%. The combination of inexpensive fluorescein (5 mol%) as photosensitizer and simple thiourea (20 mol%) additive provides an environmentally friendly alternative to expensive transition metal complexes, which proceeds under mild conditions and tolerates air and moisture. We observed that fluorescein without thiourea additive gave product in 84% yield, while thiourea even in absence of fluorescein is also able to assist in formation of product and with good yield of 75%. This is evidence for a cooperative effect of fluorescein and thiourea if employed together. Iminium ion **IV** can be formed from radical cation **II** by deprotonation to **III**, followed by an oxidation step (***Path 1***) or by a homolytic pathway (***Path 2***). Computationally, ***Path 1*** has been found to be thermodynamically preferred. We propose that the role of thiourea comprises of its function as radical scavenger (to prevent overoxidation of the substrate, of the intermediate species and photobleaching of fluorescein) as well as its possible mediation of singlet oxygen formation. In addition, we found through addition of NaN_3 as selective quencher of $^1O_2$, that singlet oxygen must be crucially involved in formation of product. Computationally, formation of iminium ion **IV** by the thermodynamically most preferred pathway proceeds via reaction, either with singlet oxygen, or with excited state fluorescein (***Path 1***, ***step 2***). This convenient, time-saving, and cost-reducing C–H functionalization procedure allows easy access to new bioactive tetrahydroisoquinoline-butenolide hybrids that can also be used for further synthetic transformations towards tetrahydroisoquinoline-γ-butanolides. Notably, *in vitro* studies of selected tetrahydroisoquinoline-butenolide hybrid compounds demonstrated high antischistosomal activities, which makes them novel potential drug candidates. In addition, studied novel tetrahydroisoquinoline-butenolide hybrids exhibited low EC_{50} values, which are comparable to those of standard anticancer drugs which were tested *in vitro* against a panel of human cancer cell lines (DU 145 (human prostate cancer), SKOV3 (human ovarian cancer), MCF-7 (human breast cancer), A549 (human lung cancer), HELA (human cervical cancer)), without causing any harm to normal cells (HEK293). Thus, the obtained products have a high potential for pharmaceutical applications.

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Keywords: Domino reaction • visible light • metal-free C–H functionalization • tetrahydroisoquinoline-butenolide hybrids • antischistosomal and anti-cancer activities • DFT calculations

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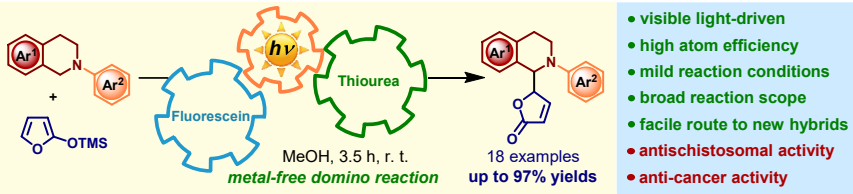

A facile metal-free visible light-driven amine oxidation/vinylogous Mannich two-step domino reaction was developed. Both experimental and computational evidence supported the crucial role of singlet oxygen in the developed C–H functionalization reaction. This straightforward, waste reducing and cost-effective method is highly appealing for synthesis of new antischistosomal and anti-cancer agents.