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Facile preparation of tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazines via reductive cyclization of 2-(8-quinolinyloxy) ethanones and their antioxidant activity

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ABSTRACT

Pd/C-catalyzed reductive cyclization of 1-aryl-2-(8-quinolinyloxy)ethanones opens a facile access to the title compounds in good yields. The scope of this reductive cyclization is explored and the antioxidant activities of the products are studied.

Heterocyclic rings are the fundamental components of more than half of the biologically active natural compound's skeleton.[1] Investigations towards understanding the reactivity of heterocyclic compounds are therefore gaining attention of chemists towards the synthesis of *N*-heteroaromatics, and great efforts have been made to discover and optimize new reactions that facilitate the construction of novel *N*-heterocycles. A facile and efficient route for synthesis of a new family of heterocycles open possibility to discover new types of biologically active units that can be used in the generation of library of compounds, or for use in the development of novel methodologies to be applied in organic synthesis.

In recent years, a rapid development in the chemistry of 1,2,3,4-tetrahydroquinoline (THQ) and its derivatives has been observed.[2] The substituted THQ moiety is present in many pharmacologically active compounds.[3–7] Tetrahydroquinolines are already in use and have been identified as potential drugs against many diseases.[8–10] These compounds shows antihypertensive,[11] oxytocin antagonist,[12] vasopressin antagonist,[13] and calcium antagonist[14] activity. Besides pharmaceutical applications, THQ derivatives are useful as pesticides,[15] antioxidants,[16] corrosion inhibitors,[17] and active component of various dyes.[18] In addition, they have application as hole transporting materials for electrophotography.[19,20] Tricyclic oxazino-fused tetrahydroquinolines have gained attention as cannabinoid receptor agonists for potential therapeutic targets of inflammatory, neuropathic pain[21] and as several antibiotics such as ofloxacin, levofloxacin, pazufloxacin, etc. Although the antioxidant activities of quinolines and 1,4-dihydropyridines[22,23] have been extensively studied, the tricyclic oxazino-fused tetrahydroquinolines/benzoxazines are not well explored.

Hydrogenation of organic molecules is one of the most useful processes, most commonly it is carried out in either a homogeneous[24] or a heterogeneous[25] catalytic system, which involves H_2 and a transition metal. Two of the most common methods to prepare amines are the reductive amination of carbonyl compounds and the hydrogenation of nitriles. The reductive amination is often being performed by using formic acid (Leuckart–Wallach reaction)[26] or certain metal hydrides,[27] later on sodium cyanoborohydride appears to be the most convenient reagent.[28] However the reductive amination using Pd/C with or without a co-catalyst are also known.[29,30]

Free radicals play an important role in numerous biological processes, such as the intracellular killing of bacteria by phagocytic cells.[31] Excessive amounts of free radicals can also lead to damage to biomolecules such as lipids, proteins, enzymes, and DNA in cells and tissues.[32] This may result in cancer, diabetes, cardiovascular diseases, autoimmune diseases, myocardial infarction, neurodegenerative disorders, aging, and various other diseases are caused because of their violent reactivity.[33–35] The antioxidants can minimize or inhibit the oxidative damage through interrupting the free radical formation or terminating the chain reaction. Thus, identification and development of novel antioxidants to prevent radical induced damage have attracted the attention of chemists and medical scientists. To the best of our knowledge there is no report on

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the evaluation of antioxidant activity of tricyclic oxazino-fused-tetrahydroquinolines/benzoxazines. In continuation of our research work aimed towards the development of new strategies for the synthesis of organic compounds,[36] we were encouraged to design a convenient and efficient route to synthesize novel tricyclic oxazino-fused-tetrahydroquinoline/benzoxazine compounds, which are having promising antioxidant activity.

Phenacylbromides **6a–m** were prepared by our method reported earlier.[36a] Further O-alkylation of 8-hydroxyquinoline with phenacyl bromide using K_2CO_3 in DMF had resulted in 1-phenyl-2-(quinolin-8-yloxy)ethanone (**5a**).[37] Analogously, the O-alkylated derivatives **5b–m** were prepared in 80–90% yield (see Supplementary data). Compound **5a** was subjected to hydrogenative cyclization over 20% Pd/C to get the desired 3-phenyl-2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine (**4a**, Scheme 1). The plausible rationale for formation of product is shown in Scheme 2.

We optimized the reaction conditions (reaction time, pressure and catalyst loading) to achieve maximum conversions (Tables 1 and 2). The time required for reaction completion was 3 h. Using methanol as solvent and 20 wt % catalyst loading at room temperature, we performed different reactions systematically varying pressure of reaction viz 100, 150, 200, 250 psi and results are given in Table 1. In all cases good to excellent conversions were obtained. However, conversion increases with pressure up to 200 psi and then decreases. Maximum conversions 99.7% and 98.9% were achieved at 150 and 200 psi pressure, respectively (Table 1, entries 2 and 3). However, yield of the desired product **4a** increased with pressure, and was 85.2% at 250 psi (Table 1). Based on these results, the reaction pressure was fixed at 200 psi for further studies. We optimized the conversion of **5a** by varying the catalyst loading while keeping other parameters such as temperature, time and pressure constant, and results are shown in Table 2. Maximum conversion (98.9%) was achieved at 20 wt % catalyst loading. However the yield was increased with catalyst loading up to 20 wt % of catalyst.

Maximum yield 79.3% for **4a** was observed at 20 wt % of catalyst. In order to investigate the general applicability of this methodology, we employed various substituted 1-aryl-2-(quinolin-8-yloxy)ethanone (**5a–m**) and performed reactions at optimized reaction conditions, results are given in Table 3. In all cases the tricyclic compounds **4a–m** were isolated in good to excellent yields (see Table 3, entries 1–5 for R^1 = aryl, entries 6–10 for R^1 = alkoxylated phenyl). It is noteworthy, however, that for R^1 = 3-(4)-aminophenyl or 2-thienyl slightly lower yields were obtained, which may be due to a decrease in activity of the catalyst through coordination with N and S lone pairs (entries 11–13).

Table 1
Effect of pressure on the reductive cyclization of 1-phenyl-2-(quinolin-8-yloxy)ethanone (**5a**)

Entry	Pressure (psi)	Conversion of **5a** (%)	Yield of **4a** (%)
1	100	75.4	63.5
2	150	99.7	63.7
3	200	98.9	79.3
4	250	82.8	85.2

Reaction conditions: substrate **5a**: 50 mg (0.19 mmol), catalyst: 20% Pd/C, rt, time: 3 h.

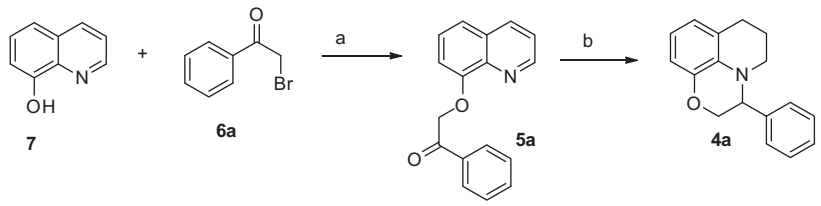
Table 2
Effect of catalyst wt % on the reductive cyclization of 1-phenyl-2-(quinolin-8-yloxy)ethanone (**5a**)

Entry	Catalyst (wt %)	Conversion of **5a** (%)	Yield of **4a** (%)
1	10	96.7	60.8
2	20	98.9	79.3
3	30	96.2	75.8

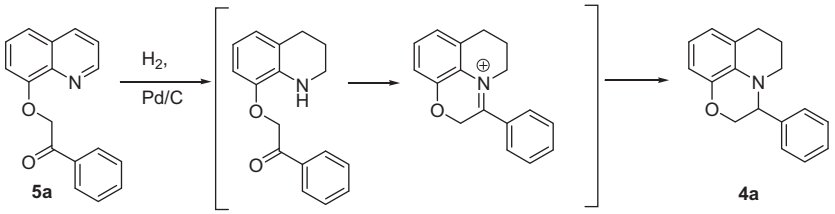
Reactions conditions: substrate **5a**: 50 mg (0.19 mmol), rt, time: 3 h, pressure: 200 psi.

Antioxidant activities of the synthesized THQs were measured against 2,2-diphenyl-1-picrylhydrazyl (DPPH),[38] and 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulfonate) cation ($ABTS^+$)[39] radicals as described earlier. DPPH and ABTS radical scavenging activity are the most commonly used methods for screening the antioxidant activities of the various natural as well as synthetic antioxidants. The IC_{50} values, that are the concentration required to scavenge 50% of the radicals, were calculated to evaluate the potential antioxidant activities. The IC_{50} of butylated hydroxytoluene (BHT) and ascorbic acid were also determined for comparison. The results were summarized in Table 4.

It can be seen from Table 4 that compounds **4g**, **4h**, and **4l** showed better radical scavenging activities than the synthetic

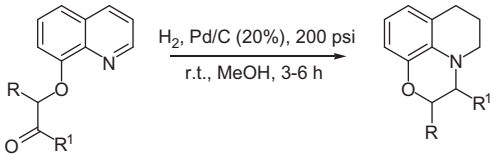


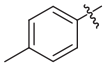
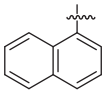
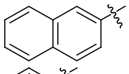
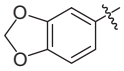
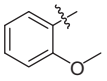
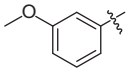
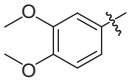
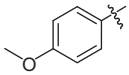
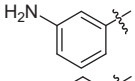
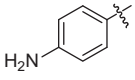
Scheme 1. Synthesis of tricyclic oxazino-fused-tetrahydroquinoline/benzoxazine (**4a**). Reagents and conditions: (a) K_2CO_3, DMF, rt, 4 h, 90%; (b) H_2, Pd/C (20%), MeOH, 200 psi, rt, 3 h, 70%.



Scheme 2. Plausible rationale for reductive cyclization.

Table 3
Preparation of fused tetrahydroquinolines **4a–m** using H_2, Pd/C



Entry	Compd	R	R^1	Time (h)	Yield[a] (%)
1	**4a**	H		3	70
2	**4b**	H		3	75
3	**4c**	H		3	75
4	**4d**	H		3	77
5	**4e**	CH_3		3	73
6	**4f**	H		3	80
7	**4g**	H		3	72
8	**4h**	H		3	76
9	**4i**	H		3	78
10	**4j**	H		3	73
11	**4k**[b]	H		6	65
12	**4l**[b]	H		5	64
13	**4m**	H		6	66

Reaction conditions: substrate **5a**: 200 mg (0.76 mmol), rt, time: 3 h, pressure: 200 psi.
[a] Isolated yield.
[b] NO_2 in the original substituent R^1 in **5k**, **l** was converted to NH_2, at 50 °C.

commercial antioxidants ascorbic acid and BHT, with IC_{50} values of 45.4, 44.6 and 45.0 μM, respectively, while compounds **4k** and **4m** shows better activity than BHT with IC_{50} value of 52.3 and 56.3, respectively. Compounds **4a**, **4c**, **4f**, **4i**, and **4j** displayed effective DPPH radical scavenging activity close to BHT, with IC_{50} of 78.8, 75.2, 75.5, 78.3 and 64.5 μM, respectively. Compound **4b** exhibited low DPPH radical scavenging activity and its IC_{50} was found to be 98.4 μM. These results depict that electron donating groups on the phenyl ring enhance the activity (Scheme 3). For example, the mono methoxy or amino functionality on the phenyl ring appeared to be major contributors to the DPPH radical scavenging activities, whereas the naphthyl substituted compounds exhibited lower activity due to the withdrawing effect of the napthyl group, which destabilizes the free radical. The formation of radical shown in Scheme 3 was further confirmed by DFT calculations (Table 5)

Table 4
Radical scavenging activities of compounds **4a–m** (mean values from triplicate tests)

Compds	DPPH· IC_{50} (μM)	$ABTS^{\cdot+}$ IC_{50} (μM)
4a	78.8 ± 0.5	38.3 ± 1.5
4b	98.4 ± 1.5	48.4 ± 2.4
4c	75.2 ± 2.3	52.4 ± 1.7
4d	98.3 ± 3.1	62.2 ± 2.6
4e	95.4 ± 5.1	62.4 ± 2.1
4f	78.3 ± 2.3	42.5 ± 2.2
4g	45.4 ± 0.2	15.3 ± 0.8
4h	44.6 ± 0.5	9.3 ± 0.9
4i	75.5 ± 1.1	28.4 ± 1.3
4j	64.5 ± 0.6	26.7 ± 0.7
4k	52.3 ± 1.0	17.8 ± 0.8
4l	45.0 ± 0.6	10.0 ± 0.4
4m	56.3 ± 0.7	20.2 ± 0.9
Ascorbic acid	49.7 ± 0.2	18.3 ± 0.2
BHT	63.1 ± 0.5	32.1 ± 0.4

using Gaussian 09.[40] Enthalpy values indicated the ease of formation of radical A as compared to the other possible radicals. The formation of radical A ($\Delta_f H°$ −84.5444 kcal/mol) was less endothermic than the radical B ($\Delta_f H°$ −88.4113 kcal/mol), whereas formation of radical C and dimerization of radical A was highly exothermic ($\Delta_f H°$ 668.1176 and 1421.466 kcal/mol, respectively). The HOMO–LUMO energy gap of radical A was smaller than the B, C and dimer of A, which impacts the ease of radical formation in the compound A.

$ABTS^+$ radical assay is a conventional and excellent model for assessing the antioxidant activities of hydrogen-donating and chain breaking antioxidants.[41] It was found from Table 4 that most compounds showed good inhibition of $ABTS^+$ radical. Compounds **4g–m** exhibited better $ABTS^+$ radical scavenging activities than the synthetic commercial antioxidant BHT, with IC_{50} of 15.3, 9.3, 28.4, 26.7, 17.8, 10.0 and 20.2 μM, respectively. Besides, compounds **4g**, **4h**, **4k** and **4l** displayed better radical scavenging activities than ascorbic acid. Obviously, of these compounds, **4h** showed the best $ABTS^+$ radical scavenging activity, while compound **4e** showed the lowest activity with IC_{50} value 62.4 μM. From these observations, we can conclude that the phenyl ring having methoxy or amino functionality showed promising $ABTS^+$ radical scavenging activity.

In summary, we have developed a general and practical protocol for the synthesis of the tricyclic oxazino-fused THQ/benzoxazine core by reductive cyclization using commercially available reagents: Pd/C, 8-hydroxyquinone, α-haloketones. This method offers several salient features such as rapid conversion, operation simplicity, moderate to good yields, great synthetic flexibility, and formation of structurally unique molecules with antioxidant activity. Among the compounds screened, it is conceivable that derivatives showing promising antioxidant activity can be further modified to maximize their potency.

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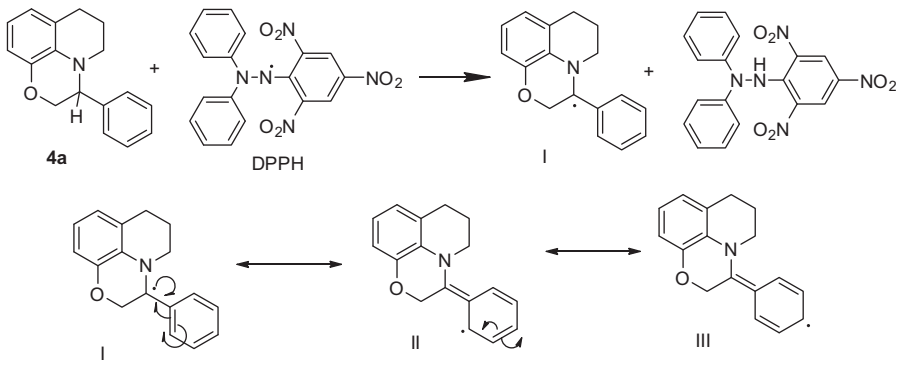
Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.09.088.



Scheme 3. Proposed rationale of reaction of oxazino fused tertrahydroquinolines/benzoxazines with DPPH.

Table 5
Enthalpy of Formation of radicals for THQ derivatives and HOMO–LUMO gap

Radicals	DFT optimized structures	$\Delta_f H°$/(kcal mol^{-1})	HOMO–LUMO gap (kcal mol^{-1})
A		−84.5444	−46.4922
B		−88.4113	−52.9116
C		686.1176	−86.3767
Dimer of A		1421.466	−98.519

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