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Green synthesis and antioxidant activity of novel series of benzofurans from euparin extracted of *Petasites hybridus*

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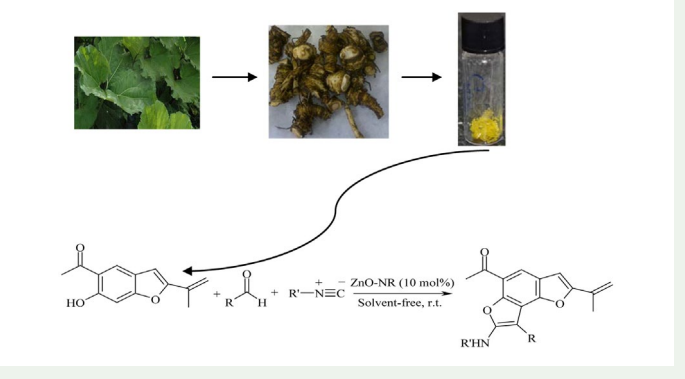
ABSTRACT

A novel class of benzofuran derivatives is prepared from the isocyanide-based MCR, euparin and aldehydes in the presence of ZnO-nanorods as a catalyst in excellent yields at room temperature under solvent-free conditions as a green reaction medium. Also, the antioxidant activities of some synthesised compounds such as **4a**, **4b**, **10a** and **10b** were evaluated by DPPH radical scavenging and ferric reduction activity potential (FRAP) assays. Compound **10b**, was shown moderate radical scavenging activity and very good reducing activity compared to standards (BHT and TBHQ).



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Benzofuran; isocyanide; ZnO-nanorods; three-component reaction; euparin

1. Introduction

Multicomponent reactions (MCRs) are described as one-pot procedures that unite as a minimum three reactants to form a single product, including fundamentally all the atoms of the reactants (Zhu and Bienayme 2005; Dömling 2006; Ganem 2009; Ruijter et al. 2011; Hajishaabanha et al. 2016). Also, Green chemistry is a rapidly expanding new field that gives us a practical path for the stable development of future science and technologies (Varma

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1999). Green chemistry employs highly effective and environmental favourable synthetic methods for going to live without drugs, accelerating the optimisation of the drug discovery process with a decrease without environmental effects. Green chemistry also presents improved chemical procedure financials associated with a decrease environmental capacity. There has been a developing attention over the past years with the expansion of new and efficient preparative procedures for the synthesis of substituted heterocycles because of the important position of a variety of heterocycles in the functions of biologically significant molecules (Murata and Yasumoto 2000; Ismabery and Lavila 2008; Alcaide et al. 2010; Dondoni 2010). Benzofuran units are an important class of heterocyclic compounds exhibiting remarkable biological activities. Among the many known heterocyclic compounds, benzofuran shows biological activity on an unexpectedly high number of targets (Teimouri and Khavasi 2007; Nevagi et al. 2015; Sajjadi-Ghotbabadi et al. 2017). It exists in various bioactive natural products, polymers and pharmaceuticals (De Luca et al. 2009). Drugs, including benzofuran rings are in medical employ for the therapy of cardiac arrhythmyas, urinary incontinence, mild Alzheimer disease, opioids overdose, tuberculosis infections, hypertension and heart failure and syndrome (Nevagi et al. 2015). Benzofurans are reported active as plant growth regulators (Rentzea et al. 1983), insecticides (Jacobsen and Crosby 1971), herbicides (Sasaki et al. 1992), anti-inflammatory (Xie et al. 2014), anticancer (Flynn et al. 2002), anti fungi (Telvekar et al. 2012), antibacterial (Bandgar et al. 2010), antimalarial (Yu et al. 2012) and antiviral agents (Whitby et al. 2009). General synthetic methods for the synthesis of substituted benzofurans include the adjustment of different arenes (Yamashita et al. 1989; Sakamoto et al. 1991 Saku et al. 2010) with the creation of carbon–oxygen bond (Willis et al. 2004; Anderson et al. 2006**)** or through a transition–metal catalysts (Watanabe et al. 2000; Ackermann and Kaspar 2007; Bernini et al. 2007; Gabriele et al. 2007; Nagamochi et al. 2007; Cho et al. 2008). At the present time, due to a growth in environmental consciousness in chemical research and industry, concentration of researchers has been focused on the use of reusable heterogeneous catalysts in organic conversions (Hu and Long 2016). Heterogeneous catalysts have some advantages, such as ease of separation from the reaction mixture, ability of recycling, non-toxicity, ease of use, storage safety, long lasting, and acceptance of a broad range of temperatures and pressures (Kouzu et al. 2008; Radhakrishan et al. 2011; Rateb et al. 2014). Herein, we display an efficient synthesis of benzofuran derivatives in good yield via the reaction of 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone **1** (Khaleghi, Bin Din, Jantan, et al. 2011, Khaleghi, Bin Din, Rostami Charati, et al. 2011, Khaleghi et al. 2014; Dastoorani, Maghsoodlou, Khalilzadeh, García-Granda, et al. 2016; Dastoorani, Maghsoodlou, Khalilzadeh, Sarina 2016), aldehydes **2** and isocyanides (Rostami-Charati et al. 2012) **3** in the presence of catalytic amount of ZnO–NR under solvent-free conditions at room temperature (Scheme S1).

2. Results and discussion

2.1. Chemistry

In this research one of the starting materials is natural and has biological activity that is reported in the literature (Khaleghi, Bin Din, Rostami Charati, et al. 2011). Also these reactions were performed under green conditions and room temperature but other methods performed under high temperature such as 120 °C. Because of euparin have biological activity maybe products of

these reactions have biological activity that we performed only antioxidant activity of some synthesised compounds.

For the optimisation of reaction conditions, several solvent such as CH_3CN, toluene, CH_2Cl_2, H_2O, DMF and solvent-free condition are employed. Among them, solvent-free conditions are the best (Table S1).

Also, several catalysis such as ZnO-nanoparticles, ZnO-nanorods, TiO_2–NPs, CuO–NPs, ZnO–CM, Fe_3O_4–MNPs and KF/CP NPs is investigated and among them, ZnO–NR are the best (Table S2). By increasing the amount of ZnO–NR from 10 to 35%, the yield of **4a** did not show any significant increase. As a result, 10 mol% ZnO–NR was selected as optimum amount.

The reusability is one of the significant properties of this catalyst. After the reaction was complete, the catalyst was separated and then washed with ethyl acetate, air-dried, and employed directly under the same conditions without further purification. It was shown that the catalyst could be employed for five runs without considerable decrease in the yield of product and its catalytic activity (Table S3). ZnO–NR is prepared according to the literature report (Sabbaghan et al. 2012; Shaterian and Mohammadnia 2013). The morphology of the ZnO–NR was confirmed by SEM (Figure S1) and XRD pattern of ZnO–NR is demonstrated in Figure S2 (Sabbaghan et al. 2012; Shaterian and Mohammadnia 2013). The length and diameter of nanorods were 300–600 and 50–70 nm, respectively.

The 1:1 intermediate obtained from the addition of 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone **1** to the aldehydes **2** in the presence of ZnO–NR. ZnO–NR has Lewis acid sites (Zn^{2+}) and Lewis basic sites (O^{2-}) (Hosseini-Sarvari et al. 2008; Hosseini-Sarvari and Tavakolian 2012). In this reaction, the Zn^{2+} sites are interacting with carbonyl groups in aldehyde and euparin and O^{2-} site of ZnO nanostructures taking up a proton of **8** to generate **4** (Scheme S2) (Hosseini-Sarvari and Tavakolian 2012).

This intermediate was reacted with isocyanide to produce benzofuran derivatives **4**. The structures of compounds **4a**–**f** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, in the ^{1}H NMR spectrum of **4a** exhibited one singlet for CMe_3 protons at (δ 1.28 ppm), two singlets for methyl protons at (δ 2.15 and 2.68 ppm), two singlets for methin proton at (δ 5.34 and 7.82 ppm) and one singlet for NH proton at 10.52 ppm. The ^{13}C NMR spectrum of **4a** displayed one carbonyl resonance at 191.4 ppm in agreement with the proposed structure.

Probably, the intermediate **6** formed from 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone **1** and aldehydes **2** in the presence of catalytic amount of ZnO–NR. Isocyanides **3** attack as nucleophiles to intermediate **6** and produce intermediate 7 which undergo intramolecular cyclisation reaction and produce intermediate **8**. Finally, by a shift of hydrogen compound **4** is produce (Scheme S2).

Under similar conditions, the reaction of 2-hydroxy acetophenone **9**, aldehydes **2** and isocyanides **3** in the presence of catalytic amount of ZnO–NR under solvent-free conditions at room temperature that produce benzofuran derivatives **10** in good yield (Scheme S3).

2.2. Antioxidant activity evaluations

2.2.1. DPPH radical scavenging activity

The use of DPPH free radicals is one of the ways of estimating the antioxidant activities of material, especially with the natural foundation (Asseid et al. 1990). Figure S3 summarises the mean values of DPPH radical-scavenging ability of **4a**, **4b**, **10a** and **10b** from 200 to

1000 ppm concentrations compared to the synthesis antioxidants namely BHT and TBHQ. My synthesised compounds have not phenolic OH group but BHT have phenolic OH group and have more acidic property than synthesised compounds and separated by DPPH easily. The results were revealed that the type and concentration of the sample were an effective factor in the DPPH scavenging activity ($p < 0.05$) (Figure S3). Overall, the DPPH free radical-scavenging value was increased by increasing the concentration of different samples as well as the synthetic antioxidants. For example, concentration 1000 ppm of **10b** had 21.28% inhibition while 200 ppm of that was exhibited 6.91% free radical inhibition. At 400–1000 ppm concentrations between **4a**, **4b**and **10a** as well as BHT and TBHQ, there were no significant differences (Figure S3). Generally, the DPPH scavenging power was achieved TBHQ > BHT > **10b** > **10a** ≈ **4a** ≈ **4b**, respectively (Figure S3). Finally, **10b**, was shown moderate radical scavenging activity, while **4a**, **4b** and **10a** had weak radical scavenging power than to BHT and TBHQ.

2.2.2. Ferric ions (Fe^{3+}) reducing potential (FRAP)

Reducing potential of the synthesised compounds was indicated by measuring of the reduced amount of Fe^{3+}/ferri cyanide complex to the Fe^{2+}/ferrous form at 700 nm (Saundane and Nandibeoor 2015). The reducing ability of **4a**, **4b**, **10a** and **10b** compounds compared with synthetic antioxidants (BHT and TBHQ) are shown in Figure S4. The Fe^{3+} reducing the ability of benzofuran derivatives is a sign of electron transfer by them. The higher absorbance of the compounds causes the greater reducing potential. The reducing activity trend of samples was as follows:

TBHQ > BHT > **10b** > **4b** > **4a** ≈ **10a**. The results were shown that type and concentration of the sample were effectual factor on the Fe^{3+} reducing potential ($p < 0.05$) (Figure S4). In all them, the increasing concentration was enhanced ferric ions reducing potential. Compound **10b**, was revealed very good reducing activity compared to standards (BHT and TBHQ). Even at 1000 ppm concentration, **10b** had a more reducing ability than to BHT. But, the **4b**, **4a** and **10a** samples had weak reducing activity than to **10b**, BHT and TBHQ.

3. Experimental

Experimental section (experimental procedure for the synthesis of compounds **4a–f** and **10d** using spectral data and antioxidant assay) is available in supplementary material.

4. Conclusion

We report an efficient, green and environmentally benevolent procedure involving 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone **1**, aldehydes **2** and isocyanides **3** in the presence of catalytic amount of ZnO–NR under solvent-free conditions at room temperature which produce functionalized benzofurans. The present method has the advantage involving the mild and clean reaction condition, low catalyst loading, mixed reactants without any prior activation or modification, high yield and short reaction time. Also, the antioxidant activities of **4a**, **4b**, **10a** and **10b** compounds were evaluated by DPPH radical scavenging and ferric reduction activity potential (FRAP) assays. Compound **10b**, was shown moderate radical scavenging activity, while **4a**, **4b** and **10a** had weak radical scavenging power than to BHT and TBHQ. Compound **10b,** was revealed very good reducing activity

compared to standards (BHT and TBHQ). But, the **4b**, **4a** and **10a** samples had weak reducing activity than to **10b**, BHT and TBHQ.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

Ackermann L, Kaspar LT. 2007. TiCl4-catalyzed indirect anti-Markovnikov hydration of alkynes: application to the synthesis of benzo [b] furans. J Org Chem. 72:6149–6153.

Alcaide B, Almendros P, Aragoncillo C. 2010. Highly reactive 4-membered ring nitrogen-containing heterocycles: synthesis and properties. Curr Opin Drug Disc Devel. 13:685–697.

Anderson KW, Ikawa T, Tundel RE, Buchwald SL. 2006. The selective reaction of aryl halides with KOH: synthesis of phenols, aromatic ethers, and benzofurans. J Am Chem Soc. 128:10964–10965.

Asseid FM, Duke CVA, Miller JM. 1990. A^{19}F magic angle spinning nuclear magneti resonance and infrared analysis of the adsorption of alkali metal fluorides onto montmorillonite clay. Can J Chem. 68:1420–1424.

Bandgar BP, Patil SA, Korbad BL, Biradar SC, Nile SN, Khobragade CN. 2010. Synthesis and biological evaluation of a novel series of 2,2-bisaminomethylated aurone analogues as anti-inflammatory and antimicrobial agents. Eur J Med Chem. 45(7):3223–3227.

Bernini R, Cacchi S, De Salve I, Fabrizi G. 2007. Palladium-catalyzed synthesis of lipophilic benzo [*b*] furans from cardanol. Synthesis. 6:873–882.

Cho CH, Neuenswander B, Lushington GH, Larock RC. 2008. Parallel synthesis of a multi- substituted benzo [*b*] furan library. J Comb Chem. 10:941–947.

Dastoorani P, Maghsoodlou MT, Khalilzadeh MA, García-Granda S, Torre-Fernández L, Sarina E. 2016. Diastereoselective synthesis of novel benzofuran derivatives by euparin as a natural compound with DMAD in the presence of trialkyl phosphite. Heteroatom Chem. 27(2):102–107.

Dastoorani P, Maghsoodlou MT, Khalilzadeh MA, Sarina E. 2016. Synthesis of new dibenzofuran derivatives via Diels-Alder reaction of euparin with activated acetylenic esters. Tetrahedron Lett. 57:314–316.

De Luca L, Nieddu G, Porcheddu A, Giacomelli G. 2009. Some recent approaches to the synthesis of 2-substituted benzofurans. Curr Med Chem. 16:1–20.

Dömling A. 2006. Recent developments in isocyanide based multicomponent reactions in applied chemistry. Chem Rev. 106:17–89.

Dondoni A. 2010. Heterocycles in organic synthesis: thiazoles and triazoles as exemplar cases of synthetic auxiliaries. Org Biomol Chem. 8:3366–3385.

Flynn BL, Hamel E, Jung MK. 2002. One-pot synthesis of benzo [*b*] furan and indole inhibitors of tubulin polymerization. J Med Chem. 45:2670–2673.

Gabriele B, Mancuso R, Salerno G, Costa M. 2007. Cascade reactions: a new synthesis of 2-benzofuran-2-ylacetamides by sequential Pd(0)-catalyzed deallylation-Pd(II)-catalyzed aminocarbonylative heterocyclization of 1-(2-allyloxyaryl)-2-yn-1-ols. J Org Chem. 72:9278–9282.

Ganem B. 2009. Strategies for innovation in multicomponent reaction design. Acc Chem Res. 42:372–463.

Hajishaabanha F, Shaabani S, Shaabani A. 2016. Synthesis of furan-fused quinoxaline tetracyclic scaffolds via a three-component isocyanide-based reaction. Res Chem Intermed. 42:4109–4120.

Hosseini-Sarvari M, Tavakolian M. 2012. Preparation, characterization, and catalysis application of nano-rods zinc oxide in the synthesis of 3-indolyl-3-hydroxy oxindoles in water. Appl Catal A. 441–442:65–71.

Hosseini-Sarvari M, Sharghi H, Etemad S. 2008. Nanocrystalline ZnO for knoevenagel condensation and reduction of C–C double bond in conjugated alkenes. Helv Chim Acta. 91:715–724.

Hu P, Long M. 2016. Cobalt-catalyzed sulfate radical-based advanced oxidation: a review on heterogeneous catalysts and applications. Appl Catal B: Environ. 181:103–117.

Ismabery N, Lavila R. 2008. Heterocycles as key substrates in multicomponent reactions: the fast lane towards molecular complexity. Chem Eur J. 14:8444–8454.

Jacobsen M, Crosby DG. 1971. Natural occuring insecticides. New York (NY): Dekker.

Khaleghi F, Bin Din L, Jantan I, Yaacob WA, Khalilzadeh MA. 2011. A facile synthesis of novel 1,4-benzoxazepin-2-one derivatives. Tetrahedron Lett. 52:7182–7184.

Khaleghi F, Bin Din L, Rostami Charati F, Yaacob WA, Khalilzadeh MA, Skelton B, Makha M. 2011. A new bioactive compound from the roots of *Petasites hybridus*. Phytochem Lett. 4: 254–258.

Khaleghi F, Jantan I, Bin Din L, Yaacob Wan A, Khalilzadeh MA, Abbas Bukhari SN. 2014. Immunomodulatory effects of 1-(6-hydroxy-2- isopropenyl-1-benzofuran-5-yl)-1-ethanone from *Petasites hybridus* and its synthesized benzoxazepine derivatives. J Nat Med. 68:351–357.

Kouzu M, Kasuno T, Tajika M, Sugimoto Y, Yamanaka S, Hidaka J. 2008. Calcium oxide as a solid base catalyst for transesterification of soybean oil and its application to biodiesel production. Fuel. 87:2798–2806.

Murata M, Yasumoto T. 2000. The structure elucidation and biological activities of high molecular weight algal toxins: maitotoxin, prymnesins and zooxanthellatoxins. Nat Prod Rep. 17:293–314.

Nagamochi M, Fang YQ, Lautens M. 2007. A general and practical method of alkynyl indole and benzofuran synthesis via tandem Cu- and Pd-catalyzed cross-couplings. Org Lett. 9:2955–2958.

Nevagi RJ, Dighe SN, Dighe SN. 2015. Biological and medicinal significance of benzofuran. Eur J Med Chem. 97:561–581.

Radhakrishan R, Do DM, Jaenicke S, Sasson Y, Chuah GK. 2011. Potassium phosphate as a solid base catalyst for the catalytic transfer hydrogenation of aldehydes and ketones. ACS Catal. 1:1631–1636.

Rateb NM, Elnagdy SM, Zohdi HF. 2014. Neural responses to functional and experiential ad appeals: explaining ad effectiveness. Int J Adv Res. 2:355–366.

Rentzea C, Reissenwebe G, Feuerherd KH, Jung J. 1983. An expedient synthesis of enantioenriched substituted benzofuran. Ger Pat Offen. 3:139250.

Rostami-Charati F, Hossaini Z, Khalilzadeh M. 2012. Novel isocyanide-based three-component synthesis of substituted 9Hfuro[2,3-f]chromene-8,9- dicarboxylates in water. Comb Chem High T Scr. 15:433–437.

Ruijter E, Scheffelaar R, Orru RVA. 2011. Multicomponent reaction design in the quest for molecular diversity & complexity. Angew Chem Int Ed. 50:6324–6346.

Sabbaghan M, Anaraki Firooz A, Jan Ahmadi V. 2012. The effect of template on morphology, optical and photocatalytic properties of ZnO nanostructures. J Mol Liq. 175:135–140.

Sajjadi-Ghotbabadi H, Javanshir S, Rostami-Charati F. 2017. Synthesis, characterization, and antioxidant evaluations of new 2-oxochromene and benzofuran derivatives catalyzed by KF/CP. J Heterocyclic Chem. 54:979–985.

Sakamoto T, Kondo Y, Yasuhara A, Yamanaka H. 1991. Condensed heteroaromatic ring systems. XVIII. Palladium-catalyzed cross-coupling reaction of aryl bromides with (Z)-1-ethoxy-2-tributylstannylethene and its utilization for construction of condensed heteroaromatics. Tetrahedron. 47:1877–1886.

Saku O, Saki M, Kurokawa M, Ikeda K, Uchida SI, Takizawa T, Uesaka N. 2010. Synthesis studies on selective adenosine A_{2A} receptor antagonists. Part II: synthesis and structure-activity relationships of novel benzofuran derivatives. Bioorg Med Chem Lett. 20:3768–3771.

Sasaki N, Kudo S, Endo K, Suzuki R. 1992. Chem Abstr. 117:178993v.

Saundane AR, Nandibeoor MK. 2015. Synthesis, characterization, and biological evaluation of Schiff bases containing indole moiety and their derivatives. Monatsh Chem. 146:1751–1761.

Shaterian HR, Mohammadnia M. 2013. Effective preparation of 2-amino-3-cyano-4-aryl-5,10-dioxo-5,10-dihydro-4*H*-benzo[g]chromene and hydroxyl naphthalene-1,4-dione derivatives under ambient and solvent-free conditions. J Mol Liq. 177:353–360.

Teimouri MB, Khavasi HR. 2007. One-pot three-component regioselective synthesis of linear naphtho[2,3-b]-furan-4,9-diones. Tetrahedron. 63:10269–10275.

Telvekar VN, Belubbi A, Bairwa VK, Satardekar K. 2012. Novel *N*′-benzylidene benzofuran-3-carbohydrazide derivatives as antitubercular and antifungal agents. Bioorg Med Chem Lett. 22:2343–2346.

Varma RS. 1999. Solvent-free organic syntheses using supported reagents and microwav irradiation. Green Chem. 1:43.

Watanabe M, Yamamoto T, Nishiyama MA. 2000. A new palladium-catalyzed intramolecular cyclization: synthesis of 1-aminoindole derivatives and functionalization of their carbocylic rings. Angew Chem Int Ed. 39:2501–2504.

Whitby LR, Lee AM, Kunz S, Oldstone MBA, Boger DL. 2009. Characterization of lassa virus cell entry inhibitors: determination of the active enantiomer by asymmetric synthesis. Bio org Med Chem Lett. 19:3771–3774.

Willis MC, Taylor D, Gillmore AT. 2004. Palladium-catalyzed intramolecular o- arylation of enolates: application to benzo [b] furan synthesis. Org Lett. 6:4755–4757.

Xie YS, Kumar D, Bodduri VDV, Tarani PS, Zhao BX, Miao JY, Jang K, Shin DS. 2014. Microwave-assist parallel synthesis of benzofuran-2-carboxaide derivatives bearing anti-infiammatory, analgesic and antipyretic agents. Tetrahedron Lett. 55:2796–2800.

Yamashita A, Toy A, Scahill T. 1989. Synthesis of khellin and its analogs via chromium carbene complexes. J Org Chem. 54:3625–3634.

Yu ZY, Brannigan JA, Moss DK, Brzozowski AM, Wilkinson AJ, Holder AA, Tate EW, Leatherbarrow RJ. 2012. Design and synthesis of inhibitors of *Plasmodium falciparum N*-myristoyltransferase, a promising target for antimalarial drug discovery. J Med Chem. 55:8879–8890.

Zhu J, Bienayme H. 2005. Multicomponent reactions, Wiley-VCH, Weinheim.