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Short communication

Synthesis, antiglycation and antioxidant potentials of benzimidazole derivatives

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ABSTRACT

Benzimidazole derivatives **1**–**20** were synthesized and evaluated for antiglycation and antioxidant potentials. Among the series some analogs showed antiglycating potential ranging in between 182.30 ± 1.20 and 473.51 ± 2.17 when compared with standard rutin (IC_{50} value 295.09 ± 1.04 μM) and for antioxidant potential ranging between 22.42 ± 0.26 and 82.30 ± 1.33 when compare with standard Propyl gallate (IC_{50} value 29.20 ± 1.25). Compound **2**, **6**, **10** and **19** showed potent antioxidant and antiglycation inhibitory potentials. Compounds **7**, **11**, **13**, 1**5** and **20** showed moderate antiglycating potential with IC_{50} values 473.51 ± 2.17, 325.20 ± 1.70, 440.0 ± 3.60, 370.60 ± 2.80 and 415.20 ± 3.20 μM, and these compounds also showed excellent antioxidant potential with IC_{50} values 73.51 ± 1.17, 45.63 ± 0.92, 82.30 ± 1.33, 75.41 ± 1.51, 40.60 ± 0.80 and 64.92 ± 1.41 μM respectively. The remaining compounds **1**, **3**, **4**, **5**, **8**, **9**, **12**, **14**, **16**, **17**and **18** were found inactive.

1. Introduction

Discovery of antiglycating agents is a vital tactic to cure diabetic problems, since at present, number of active antiglycating agents is neglected and there is an urgent demand of new compounds to be identified (Ahmed, 2005). As the hostile occurrence of type-2 diabetes is rising, its damaging effects are frequently abetting the production of advanced glycation end products (Brownlee, 1994). These advanced glycation end products (AGEPs) are significant pathogenic intermediaries of approximately all diabetic problems (Peppa et al., 2008). Glycation is a chaotic process which can take place endogenously (Kellow and Savige, 2013) and modifies biomolecules (Misciagna and Michele, 2007). The process is a non-enzymatic reaction of proteins with sugars (Ho et al., 2010). These modifications lead to impaired protein functions (Goodarzi et al., 2010) and perhaps contributes to microvascular diseases that slows down wound healings of diabetic patients, associated complications and aging-related sicknesses for instance cataracts, retinopathy, renal dysfunction and arteriosclerosis (Rodriguez and Jarvis, 2012; Anguizola et al., 2013; Akash, et al., 2013). Chemical entities that inhibit or slows down the process of glycation play a pivotal role in the treatment of diabetic complications. Exploration for new antiglycating agents is, therefore, still of great scientific interest (Ahmed, 2005). In recent years, certain food stuffs have been identified and attracted attention as having antiglycating and antioxidant properties (Deetae et al., 2012).

The most of diseases are linked with amplified oxidative stress due to either the changes in generation of free radicals or the changes antioxidant balanced activity (Tessier et al., 2009). The major methods of antioxidant resistance comprise enzymes CATs, SODs, and GH-PXs.

The a number of vitamins and micronutrients are energetic in reducing free-radical species or necessary as cofactors for inhibitions enzymes (Pinzani et al., 2010). Equally defensive and chain contravention antioxidants have a control over the oxidative stress that goes together with disease and aging (Jacomelli et al., 2010). Lately, The concentration in natural product antioxidants such as

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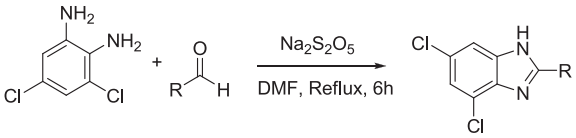
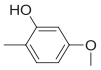
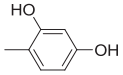
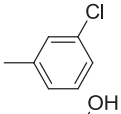
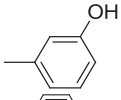
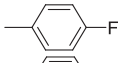
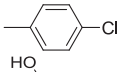
phenolic compounds and vitamin E (α-tocopherol). Mainly phenolic compounds are usually separated into flavonoids, stilbenes, tannins, phenolic acids and lignans (Dai and Mumper, 2010).

Compounds having benzimidazoles core are general and significant substructures occurring in nature and other bioactive compounds. They do something as glucagon receptor anagonists (Chang et al., 2001), β-Raf kinase (Takle et al., 2006), α-glucosidase (Taha et al. (2016a)), β-glucuronidase (Taha et al., 2015), antiglycation (Taha et al. (2016b)), CB1 cannabinoid receptor antagonists (Eyers et al., 1998), carbonic anhydrase (Khan et al., 2013a; Khan et al. (2013b)). Several imidazoles work as antibacterial (Antolini et al., 1999), antibiotics (Brogden et al., 1978) fungicides (Santo et al., 2005), anti-inflammatory agents (Brimblecombe et al., 1975), antidiabetic and antihypertensive (Pathan et al., 2006; Bellina et al., 2007).



Scheme 1. Synthesis of Benzimidazole derivatives (**1**–**20**).

Table 1
Structures of Benzimidazole derivatives (**1**–**20**).

No.	Structure	No.	Structure
1		11	
2		12	
3		13	
4		14	
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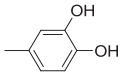
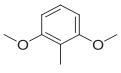
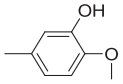
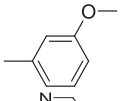
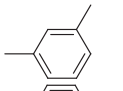
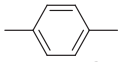
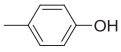
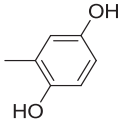
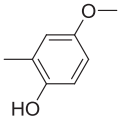
6		16	
7		17	
8		18	
9		19	
10		20	

2. Results and discussion

2.1. Chemical synthesis

Benzimidazole derivatives **1**–**20** were synthesized by treating of 3,5-dichlorobenzene-1,2-diamine with of arylaldehyde. Finally the precipitates were separated by filter and the crude product was recrystalized in ethyl acetate to afford pure crystal and characterized by different spectroscopic methods (See Scheme 1).

Benzimidazole derivatives **1**–**20** (Table 1) were subjected to various spectroscopic analysis and their data partially matched with the similar type of derivatives previously published (Alkahtani et al., 2012; Tunçbilek et al., 2009).

2.2. Biological activity

2.2.1. Antiglycation activity

All synthesized benzimidazole derivatives (**1**–**20**) were evaluated for their antiglycation potential. Among the series, compounds **2** (IC_{50} = 240.50 ± 1.30 μM), **10** (IC_{50} = 182.30 ± 1.20 μM), and **19** (IC_{50} = 288.60 ± 1.30 μM) showed most potent antiglycation activity if compared with the standard rutin (IC_{50} = 295.09 ± 1.04 μM) (Table 2). Structure activity relationships were mainly based on substitution pattern on aldehyde phenyl ring. Compound **10**, a 2,5-dihydroxy analog was found to be the most active among the series. If we compare compound **10** with compound **2**, a 2,4-dihydroxy analog, and compound **6**, a 3,4-dihydroxy, compound **10** is superior. The difference in their potential is mainly due to the position difference of substituents. The greater potential shown by these compounds might be due to the acetal formation with fructose carbonyl group. Similarly compound **19**, a *para* hydroxyl analog was found to the third most active compound among the series. The decline in the potential of this compound might be due to less number of hydroxyl group on phenyl ring if we compare it with compound **10** and **2**. By comparing compound **19** with other monohydroxy analogs like **13**, a *meta* hydroxyl analog and **15**, a *ortho* hydroxyl analog, compound **19** is superior. The difference in their potential is mainly due the position difference of hydroxyl group on phenyl ring. By bringing about other substituents like chloro, flouro or methyl group on phenyl ring makes

Table 2
Antiglycation inhibition activity of benzimidazole derivatives **1**–**20**.

No.	Antioxidant (IC_{50} ± SEM μM)	Antiglycation (IC_{50} + SEM μM)	No.	Antioxidant (IC_{50} ± SEM μM)	Antiglycation (IC_{50} ± SEM μM)
1	N.A.	N.A.	11	45.63 ± 0.92	325.20 ± 1.70
2	31.71 ± 0.42	240.50 ± 1.30	12	N.A.	N.A.
3	N.A.	N.A.	13	82.30 ± 1.33	440.0 ± 3.60
4	N.A.	N.A.	14	N.A.	N.A.
5	N.A.	N.A.	15	75.41 ± 1.51	370.60 ± 2.80
6	29.14 ± 0.47	310.20 ± 1.60	16	N.A.	N.A.
7	73.51 ± 1.17	473.51 ± 2.17	17	N.A.	N.A.
8	N.A.	N.A.	18	N.A.	N.A.
9	N.A.	N.A.	19	40.60 ± 0.80	288.60 ± 1.30
10	22.42 ± 0.26	182.30 ± 1.20	20	64.92 ± 1.41	415.20 ± 3.20
	(Propyl gallate) 29.20 ± 1.25	(Rutin) 296.20 ± 1.10		(Propyl gallate) 29.20 ± 1.25	(Rutin) 296.20 ± 1.10

SEM[a] is the standard error of the mean, NA[b] Not active, Rutin, [c] standard inhibitor for glycation activity.

it completely inactive. So, it was concluded that only those analogs showed antiglycation potential among these synthesized scaffolds which have hydroxyl group on phenyl ring. The number and position of hydroxyl further effect their potential.

2.2.2. Antioxidant activity

Benzimidazole derivatives **1**–**20** were also evaluated for their antioxidant potential. Among the series, compounds **6** (IC_{50} = 29.14 ± 0.47 μM) and **10** (IC_{50} = 22.42 ± 0.26 μM) showed potent antioxidant activity as compared to standard propyl gallate (IC_{50} = 29.20 ± 1.25 μM). The greater potential of these compounds i.e. **6,** a 3,4-dihydroxyanalogand **10,** a 2,5-dihydroxyanalogmight be due to the stabilization of phenoxy radical formed during this assay. The other dihydroxy analog like Compound **2** (IC_{50} = 31.71 ± 0.42 μM) also showed good potential. The small difference in the activities of these analogs might be due to the position difference of substituents. Other analogs like **7** (IC_{50} = 73.51 ± 1.17 μM), **11** (IC_{50} = 45.63 ± 0.92 μM), **13** (IC_{50} = 82.30 ± 1.33 μM), **15** (IC_{50} = 75.41 ± 1.51 μM), **19** (IC_{50} = 40.60 ± 0.80 μM) and **20** (IC_{50} = 64.92 ± 1.41 μM) having hydroxyl group also displayed better antioxidant activity. The difference in the activities of these compounds were mainly affected by the number and position of substituents. The remaining compounds were found inactive. The antioxidant potential of all compounds evaluated as reported Anouar et al. (2013), Khan et al. (2011, 2012), Taha et al. (2014).

3. Conclusion

In this study, benzimidazole derivatives **2** and **10** have been identified as potent inhibitors of both glycation of proteins and oxidative damages. It was found that most of the active compounds possess hydroxyl substitutions.

It was also observed that substituents such as methyl, methoxy and halides do not play any significant role in inhibiting glycation and oxidative potentials. But the halides, methoxy and methyl moiety has not role to inhibit the glycation and oxidation process. These results suggest benzimidazole class of compounds is an effective class of lead molecules that may act as dual inhibitors of both glycation of proteins and the oxidative damages caused by free radicals.

These finding suggest that benzimidazole is an effective class of compounds or a lead molecule that may act as dual inhibitors of both glycation of proteins and the oxidative damages caused by free radicals

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jksus.2018.04.003.

References

Ahmed, N., 2005. Advanced glycation end products-role in pathology of diabetic complications. Diabetes. Res. Cli. Prac. 67, 3–21.

Akash, M.S., Rehman, K., Chen, S., 2013. Role of inflammatory mechanisms in pathogenesis of type 2 diabetes mellitus. J. Cell Biochem. 114 (3), 525–531.

Alkahtani, H.M., Abbas, A.Y., Wang, S., 2012. Synthesis and biological evaluation of benzo[d]imidazole derivatives as potential anti-cancer agents. Bioorg. Med. Chem. Lett. 22 (3), 1317–1321.

Anguizola, J., Matsuda, R., Barnaby, O.S., Hoy, K.S., Wa, C., 2013. Glycation of human serum albumin. Clinica Chimica Acta 42, 64–76.

Anouar, E.H., Raweh, S., Bayach, I., Taha, M., Baharudin, M.S., Meo, F.D., Hasan, M.H., Adam, A., Ismail, N.H., Weber, J.F., 2013. Antioxidant properties of phenolic Schiff bases: structure-activity relationship and mechanism of action. J. Comput. Aided. Mol. Des. 27, 951–964.

Antolini, M., Bozzoli, A., Ghiron, C., Kennedy, G., Rossi, T., Ursini, A., 1999. Analogues of 4,5-bis (3,5-dichlorophenyl)-2-trifluoromethyl-1H-imidazole as potential antibacterial agents. Bioorg. Med. Chem. Lett. 9, 1023–1028.

Bellina, F., Cauteruccio, S., Rossi, R., 2007. Synthesis and biological activity of vicinal diaryl-substituted 1H-imidazoles. Tetrahedron 63, 4571–4624.

Brimblecombe, R.W., Duncan, W.A.M., Durant, G.J., Emmett, J.C., Ganellin, C.R., Parsons, M.E., 1975. Cimetidine-a non-thiourea H2-receptor antagonist. J. Int. Med. Res. 3, 86–92.

Brogden, R.N., Heel, R.C., Speight, T.M., Avery, G.S., 1978. Metronidazole in anaerobic infections: a review of its activity, pharmacokinetics and therapeutic use. Drugs 16, 387–417.

Brownlee, M., 1994. Glycation and diabetic complications. Diabetes 43, 836–841.

Chang, L.L., Sidler, K.L., Cascieri, M.A., Laszlo, S., Koch, G., Li, B., Maccoss, M., Mantlo, N., Okeefe, S., Pang, M., Rolando, A., Hangmann, W.K., 2001. Substituted imidazoles as glucagon receptor antagonists. Bioorg. Med. Chem. Lett. 11, 2549–2553.

Dai, J., Mumper, R.J., 2010. Plant phenolics: extraction, analysis and their antioxidant and anticancer properties. Molecules 15. 7313e7352.

Deetae, P., Parichanon, P., Trakunleewatthana, P., Chanseetis, C., Lertsiri, S., 2012. Antioxidant and anti-glycation properties of Thai herbal teas in comparison with conventional teas. Food Chem. 133, 953–959.

Eyers, P.A., Craxton, M., Morrice, N., Cohen, P., Goedert, M., 1998. Conversion of SB 203580-insensitive MAP kinase family members to drug-sensitive forms by a single amino-acid substitution. Chem. Biol. 5, 321–328.

Goodarzi, M.T., Rashidi, M., Rezaei, M., 2010. Study of nonenzymaticglycation of transferrin and its effect on iron-binding antioxidant capacity. Iran. J. Basic Med. Sci. 13, 194–199.

Ho, S.C., Wu, S.P., Lin, S.M., Tang, Y.L., 2010. Comparison of anti-glycation capacities of several herbal infusions with that of green tea. Food Chem. 122, 768–774.

Jacomelli, M., Pitozzi, V., Zaida, M., Larrosa, M., Tonini, G., Martini, A., Urbani, S., Taticchi, A., Servili, M., Dolara, P., Giovannelli, L., 2010. Dietary extra-virgin olive oil rich in phenolic antioxidants and the aging process: Long-term effects in the rat. J. Nutri. Biochem. 21, 290–296.

Kellow, N.J., Savige, G.S., 2013. Dietary advanced glycationendproduct restriction for the attenuation of insulin resistance, oxidative stress and endothelial dysfunction: a systematic review. Eur. J. Clin. Nutr. 67, 239–248.

Khan, K.M., Rahim, F., Ambreen, N., Taha, M., Khan, M., Jahan, H., Najeebullah, U., Iqbal, Shaikh A., Perveen, S., 2013a. Synthesis of benzophenonehydrazone schiff bases and their in vitro antiglycating activities. Med. Chem. 9, 588–595.

Khan, K.M., Taha, M., Rahim, F., Fakhri, M.I., Jamil, W., Khan, M., Rasheed, S., Karim, A., Perveen, S., Choudhary, M.I., 2013b. Acylhydrazide schiff bases: synthesis and antiglycation activity. J. Pak. Chem Soc. 35, 929–937.

Khan, K.M., Shah, Z., Ahmad, V.U., Khan, M., Taha, M., Rahim, F., Jahan, H., Perveen, H., Choudhary, M.I., 2011. Synthesis of 2 4 6-Trichlorophenyl hydrazones and their inhibatory potenial against glycation. Med. Chem. 7, 572–580.

Khan, K.M., Shah, Z., Ahmad, V.U., Khan, M., Taha, M., Ali, S., Perveen, S., Choudhary, M.I., Voelter, W., 2012. 2,4,6-Trichlorophenylhydrazine schiff bases as DPPH radical and super oxide anion scavengers. Med. Chem. 8, 452–461.

Misciagna, G.D., Michele, G., Trevisan, M., 2007. Non-enzymatic glycated proteins in the blood and cardiovascular disease. Curr. Pharm. Des. 13, 3688–3695.

Pathan, M.Y., Paike, V.V., Pachmase, P.R., More, S.P., Ardhapure, S.S., Pawar, R.P., 2006. Microwave-assisted facile synthesis of 2-substituted 2-imidazolines. Arkivoc 15, 205–210.

Peppa, M., Uribarri, J., Vlassara, H., 2008. Glucose advanced glycation end products, and diabetes complications: what is new and what is works. Clin. Diabetes 21, 186–187.

Pinzani, P., Petruzzi, E., Magnolfi, S.U., Malentacchi, F., De Siena, G., Petruzzi, I., Motta, M., Malaguarnera, M., Marchionni, N., Pazzagli, M., 2010. Red or white wine assumption and serum antioxidant capacity. Arch. Gerontol. Geriatrics 51, 72–74.

Rodriguez, B.J., Jarvis, S.P., 2012. Atomic force microscopy: an enabling nanotechnology for diabetes research. In: Le, L.A., Hunter, R.J., Preedy, V.R. (Eds.), Nanotechnology & Nanomedicine in Diabetes. Science Publishers, Enfield, New Hampshire, pp. 34–58.

Santo, R.D., Tafi, A., Costi, R., Botta, M., Artico, M., Corelli, F., Forte, M., Caporuscio, F., Angiolella, L., Palamara, A.T., 2005. Antifungal agents.Nsubstituted derivatives of 1-[(aryl)(4-aryl-1H-pyrrol-3-yl)methyl]-1H-imidazole: synthesis, anti-Candida activity, and QSAR studies. J. Med. Chem. 48, 5140–5153.

Taha, M., Ismail, N.H., Imran, S., Rashwan, H., Jamil, W., Ali, S., Kashif, S.M., Rahim, F., Salar, U., Khan, K.M., 2016a. Synthesis of 6-chloro-2-Aryl-1H-imidazo [4, 5-b] pyridine derivatives: Antidiabetic, antioxidant, β-glucuronidase inhibiton and their molecular docking studies. Bioorg. Chem. 65, 48–56.

Taha, M., Ismail, N.H., Imran, S., Selvaraj, M., Rashwan, H., Farhanah, F.U., Rahim, F., Selvarajan, K.K., Ali, M., 2015. Synthesis of benzimidazole derivatives as potent β-glucuronidase inhibitors. Bioorg. Chem. 61, 36–44.

Taha, M., Ismail, N.H., Imran, S., Mohamad, M.H., Wadood, A., Rahim, F., Saad, A., Rehman, S.M., Khan, K.M., 2016b. Synthesis, α-Glucosidase inhibitory,

cytotoxicity and docking studies of 2-Aryl-7-methylbenzimidazoles. Bioorg. Chem. 65, 100–109.
Taha, M., Ismail, N.H., Jamil, W., Rashwan, H., Kashif, S.M., Sain, A.A., Adenan, M.I., Anouar, E.H., Ali, M., Rahim, F., Khan, K.M., Khan, M., 2014. Synthesis of novel derivatives of 4-methylbenzimidazole and evaluation of their biological activities. Eur. J. Med. Chem. 84, 731–738.
Takle, A.K., Brown, M.J.B., Davies, S., Dean, D.K., Francis, G., Gaiba, A., Hird, A.W., King, F.D., Lovell, P.J., Naylor, A., Reith, A.D., Steadman, J.G., Wilson, D.M., 2006. The identification of potent and selective imidazole-based inhibitors of B-Raf kinase. Bioorg. Med. Chem. Lett. 16, 378–381.
Tessier, D.M., Khalil, A., Trottier, L., Fulop, T., 2009. Effects of vitamin C supplementation on antioxidants and lipid peroxidation markers in elderly subjects with type 2 diabetes. Arch. Gerontol. Geriatrics 48, 67–72.
Tunçbilek, M., Kiper, T., Altanlarc, N., 2009. Synthesis and in vitro antimicrobial activity of some novel substituted benzimidazole derivatives having potent activity against MRSA. Euro. J. Med. Chem. 44 (3), 1024–1033.