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Synthesis of Novel Benzimidazole-2-carboxamide Derivatives and *in Vivo* Antihyperlipidemic Activity Evaluation

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Hyperlipidemia is known as an elevation of plasma lipid components. It contributes significantly to atherosclerosis which is one of the most important causative factors in cardiovascular diseases. Agents that cause a dramatic decrease in serum lipid levels are of great value in the treatment of cardiovascular diseases. For this purpose, a new series of benzimidazole propyl carboxamide benzophenone derivatives have been synthesized (7, 8, and 9). These compounds were tested *in vivo* to evaluate their potential hypolipidemic activity using Triton WR-1339 induced hyperlipidemic rats. All the synthesized compounds have proved to be highly biologically active, with compound 9 being the most active derivative.

Key words hyperlipidemia; Triton WR-1339; benzimidazole; low-density lipoprotein (LDL); cardiovascular disease

Hyperlipidemia is a lipid metabolism disorder characterized by increased levels of blood total cholesterol (TC), triglycerides (TGs), very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) along with decreased levels of high-density lipoprotein (HDL).[1)] It is one of the major risk factors involved in the pathogenesis of atherosclerosis and heart coronary disease development.[2,3)] Multiple clinical evidence has demonstrated that hypercholesterolemia and elevated plasma TGs levels are implicated in the development of cardiovascular diseases (CVDs).[4)] CVDs are the most common cause of death and disability worldwide.[1,5,6)] Numerous epidemiological studies have clearly demonstrated that pharmacological lowering of TC and LDL is associated with a significant reduction in clinical cardiovascular events. This has been shown in patients with established chronic heart disease (CHD) and in patients suffering familial hypercholesterolemia, where aggressive reduction in the lipid levels resulted in decreased CVDs incidence.[7)] Currently, many drugs are commercially available lowering serum cholesterol and triglycerides but with serious side effects such as elevations in hepatic transaminase enzymes, myopathy, muscle pains, and rhabdomyolysis.[8–10)] The need to develop new agents with fewer side effects has attracted a lot of research in this field. A large number of carboxamide containing different aromatic heterocyclic nuclei were prepared and evaluated for their hypolipidemic activity. Indole derivatives such as *N*-(benzoylphenyl)-5-substituted-1*H*-indole-2-carboxamides, *N*-(benzoylphenyl)-1*H*-indole-2-carboxamides,[11–14)] benzofuran derivatives like *N*-(benzoylphenyl) and *N*-(acetylphenyl)-1-benzofuran-2-carboxamides[15,16)] and benzthiophene derivatives like *N*-(pyridin-3-yl)-benzothiophene-2-carboxamide.[17)] All the previously developed carboxamide derivatives have shown low water solubility and biological testing hardships.

This work reports the synthesis of novel compounds with improved pharmacokinetic and pharmacodynamics properties with respect to those previously published.[11–14)] For this purpose, the preparation of benzimidazole benzophenone carboxamide derivatives **7**, **8**, and **9** was carried out. In this series of novel compounds, it is observed the replacement of the aromatic heterocyclic rings with a more basic and potentially more water soluble benzimidazole ring (pK_a=16.4) in comparison with the pK_a values of the other aromatic heterocyclic rings (indole pK_a=21, furan pK_a=35.6, and thiophene pK_a=33) present in the previously reported carboxamide derivatives.[11–14)] This would suggest more ionization at physiological pH, with potentially improved pharmacokinetic and pharmacodynamic properties. Moreover, for the first time, a linker of two carbon atoms was introduced between the benzimidazole and benzophenone carboxamide, allowing more flexibility in the molecule conferred by the propyl chain. Such enhanced flexibility could allow a better fit between the prepared compounds and the proper target.

Experimental

Chemicals All chemicals, reagents and solvents were of analytical grade and used directly without extra purification. Chloroform, methanol, *n*-hexane, cyclohexane, ethylacetate, dimethyl formamide (DMF), dichloromethane (DCM), dimethyl sulfoxide (DMSO) and triethyl amine (TEA) purchased from Fisher Scientific, U.K. and Tedia Company, U.S.A. 2-Benzimidazolepropionic acid, 2-aminobenzophenone, 3-aminobenzophenone, 4-aminobenzophenone and Triton were purchased from Sigma-Aldrich, Germany. Filter papers (Macherey-Nagel, Germany). Tyloxapol, a non-ionic detergent, oxyethylated tertiary octyl phenol formaldehyde polymer (Triton)[18)] was purchased from Sigma-Aldrich, U.S.A.

NMR were recorded in The Hashemite University using BRUKER Ascend 300. Chemical shifts are reported in ppm related to tetramethylsilane (TMS), internal standard. Deuterated dimethyl sulfoxide (DMSO-d_6) was used as a solvent in sample preparation. ^{1}H-NMR data are reported in the following ways: chemical shift (ppm), multiplicity, coupling constant

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(Hz), number of protons and the corresponding proton(s). For initial identification of compounds, IR spectra were recorded using Shimadzu 8400 FT-IR spectrophotometer (Japan) at Faculty of Pharmacy, Al Zaytoonah University of Jordan. All tested compounds were triturated with potassium bromide (KBr) and compressed into thin film discs (ACros, Belgium). The melting point (mp) were measured using Gallenkamp melting point apparatus (Gallenkamp), U.K.). High resolution (HR)-MS were measured in negative or positive ion mode using electrospray ionization (ESI) technique by collision-induced dissociation on a Bruker APEX-IV (7 Tesla) (Billerica, MA, U.S.A.) instrument at the University of Jordan. The samples were dissolved in chloroform and acetonitrile. TLC was performed on 20×20 cm aluminum plates pre-coated fluorescent silica gel GF254 (ALBET, Germany) the TLC was visualized under UV lamp, spectroline cabinet, Model CX-20 (U.S.A.), at 254 and/or 360 nm. For the efficient and gentle removal of solvents from the samples, Rotavapor model R-114 (Buchi, Switzerland) was used.

General Procedure for the Preparation of 3-(1*H*-Benzo[*d*]imidazole-2-yl)propanoyl Chloride (3) Oxalyl chloride (**2**), (0.48 g, 3.52 mmol) was added to 2-benzimidazole propionic acid (**1**), (0.5 g, 2.62 mmol) in a flask immersed in an ice bath, followed by the addition of few drops of DMF and 15 mL of DCM. The resulting reaction mixture was refluxed under magnetic stirring for 1 h. Then the solvent and the excess oxalyl chloride were removed by evaporation and the crude acyl derivative **3** was used immediately without further purification.

3-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(4-benzoylphenyl)-propanamide (7) 3-(1*H*-Benzo[*d*]imidazole-2-yl)propanoyl chloride (**3**) (0.45 g, 2.15 mmol) was reacted with 4-aminobenzophenone (**4**) (0.8 g, 4.05 mmol) in 15 mL $CHCl_3$ and stirred for 24 h at room temperature. Followed by addition of TEA (2 mL) to give a pale brown powder precipitate after washing with CH_3OH.

Pale brown powder (0.54 g, 68%) *Rf*=0.73 ($CHCl_3$–CH_3OH, 9 : 1), mp=286°C (284–286°C) with decomposition, IR (KBr disc): *v*=3224.98 (NH-amide), 1674.21 (CO-ketone), 1597.06 (CO-amide) cm^{-1}, ^{1}H-NMR (300 Hz, DMSO-d_6) δ: 12.24 (br s, 1H, amide-H), 10.50 (s, 1H, imidazole-H), 7.80 (d, *J*=6.6 Hz, 2H, Ar-H), 7.74 (d, *J*=6.57 Hz, 2H, Ar-H), 7.71 (d, *J*=5.25 Hz, 2H, Ar-H), 7.66 (t, *J*=5.58 Hz, 1H, Ar-H), 7.55 (t, *J*=5.73 Hz, 3H, Ar-H), 7.43 (m, 1H, Ar-H), 7.11 (pseudo-d, *J*=3.69 Hz, 2H, Ar-H) 3.16 (t, *J*=5.31 Hz, 2H, CH_2), 2.99 (t, *J*=5.46 Hz, 2H, CH_2) ppm. ^{13}C-NMR (DMSO-d_6) δ: 195.0 (1C), 171.3 (1C), 154.6 (1C), 143.9 (1C), 139.7 (1C), 138.1 (1C), 134.8 (1C), 132.7 (1C), 131.6 (2C), 129.8 (3C), 128.9 (3C), 121.9 (1C), 121.27 (1C), 118.7 (2C), 111.2 (1C), 34.3 (1C), 24.20 (1C) ppm. (ESI, positive mode): *m/z* $[M+H]^+$ 370.155 (Calcd for 370.148 for $C_{23}H_{20}N_3O_2$).

3-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(3-benzoylphenyl)-propanamide (8) 3-(1*H*-Benzo[*d*]imidazole-2-yl)propanoyl chloride (**3**) (0.45 g, 2.15 mmol) was reacted with 3-aminobenzophenone (**5**) (0.8 g, 4.05 mmol) in 15 mL $CHCl_3$. The mixture was left under magnetic stirring at room temperature for 24 h. Addition of TEA (2 mL) has led to the formation of white powder precipitate after washing with CH_3OH.

White powder (0.65 g, 81.86%): *Rf*=0.68 ($CHCl_3$–CH_3OH, 9 : 1), mp=220°C (218–220°C), IR (KBr disc): *v*=3286.70 (NH-amide), 1674.21 (CO-ketone), 1658.78 (CO-amide) cm^{-1}, ^{1}H-NMR (300 Hz, DMSO-d_6) δ: 12.22 (br s, 1H, amide-H), 10.30 (s, 1H, imidazole-H), 8.04 (s, 1H, Ar-H), 7.89 (d, *J*=6.09 Hz, 1H, Ar-H), 7.74 (d, *J*=5.28 Hz, 2H, Ar-H) 7.68 (t, *J*=5.55 Hz, 1H, Ar-H), 7.57 (t, *J*=5.73 Hz, 2H, Ar-H), 7.49 (t, *J*=5.88 Hz, 2H, Ar-H), 7.4 (d, *J*=5.73 Hz, 2H, Ar-H), 7.1 (d, *J*=3.33, 2H, Ar-H), 3.13 (t, *J*=5.46 Hz, 2H, CH_2–H), 2.94 (t, *J*=5.46 Hz, 2H, CH_2–H) ppm. ^{13}C-NMR (DMSO-d_6) δ: 196.1 (1C), 171.0 (1C), 154.7 (1C), 143.7 (1C), 139.9 (1C), 137.9 (1C), 137.5 (1C), 134.8 (1C) 133.1 (1C), 130.0 (2C), 129.5 (1C), 129.0 (2C), 124.7 (1C), 123.3 (1C), 121.9 (1C), 121.3 (1C), 120.4 (1C), 118.5 (1C), 111.2 (1C), 34.2 (1C), 24.3 (1C) ppm. (ESI, positive mode): *m/z* $[M+H]^+$ 370.155 (Calcd for 370.148 for $C_{23}H_{20}N_3O_2$).

3-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(2-benzoylphenyl)-propanamide (9) To a solution of 3-(1*H*-benzo[*d*]-imidazole-2-yl)propanoyl chloride (**3**) (0.45 g, 2.15 mmol) and 2-aminobenzophenone (**6**) (0.8 g, 4.05 mmol) in 15 mL $CHCl_3$, 2 mL of TEA was added and the reaction mixture was stirred at room temperature for 24 h the formed precipitate was obtained as brown powder after several washings with methanol.

Brown powder (0.49 g, 61.7%): *Rf*=0.76 ($CHCl_3$–CH_3OH, 9 : 1), mp=230°C (228–230°C) decomposition, IR (KBr disc): *v*=3340.71 (NH-amide), 1674.21 (CO-ketone), 1604.77 (CO-amide) cm^{-1}. ^{1}H-NMR (300 Hz, DMSO-d_6) δ: 10.60 (br, 1H, amide-H), 10.30 (s, 1H, imidazole-H), 8.36 (s, 1H, Ar-H), 7.50 (m, 3H, Ar-H), 7.48 (d, *J*=5.7 Hz, 2H, Ar-H), 7.40 (m, 3H, Ar-H), 7.20 (m, 1H, Ar-H), 7.10 (m, 3H, Ar-H), 3.03 (t, *J*=5.43 Hz, 2H, CH_2), 1.20 (t, *J*=4.86 Hz, 2H, CH_2) ppm. ^{13}C-NMR (DMSO-d_6) δ: 195.5 (1C), 170.4 (1C), 154.4 (1C), 144.3 (1C), 140.4 (1C), 137.7 (1C), 136.7 (1C), 133.0 (1C), 132.2 (1C), 131.3 (1C), 130.4 (2C), 129.9 (3C), 128.6 (3C), 124.6 (1C), 124.0 (1C), 121.6 (1C), 33.8 (1C), 24.2 (1C) ppm. (ESI, positive mode): *m/z* $[M+H]^+$ 370.155 (Calcd for 370.148 for $C_{23}H_{20}N_3O_2$).

***In Vivo* Antihyperlipidemic Testing** The novel compounds **7**, **8**, and **9** were tested *in vivo* for their hypolipidemic activities using Triton WR-1339 induced hyperlipidemic rats at a dose of 30 mg/kg.

Animals and Treatment Thirty adult male Wistar rats, weighing around 200 g, were purchased from the animal house care center of Jordan University of Science and Technology, Irbid, Jordan. These rats provided spontaneous access only to tap water throughout the experimental duration (24 h). Rats were maintained in a 12 h light–dark cycle under constant humidity temperature (25±2°C).

All experiments were performed in accordance with the Guidelines of Animal Welfare Committee of the University and in accordance with the standards set forth in the eighth edition of Guide for the Care and Use of Laboratory Animals.

Triton Model of Hyperlipidemia Triton was dissolved in distilled water and administered intraperitoneally (i.p.) to the rats at a dose of 300 mg/kg in order to induce hyperlipidemia. Triton needs around 12–20 h to achieve maximum elevation of TGs level.[11]

Pharmacological Experimental Design Overnight fasted rats were randomly divided into six groups of five animals each. The first group, serving as a normal control group (NCG) received an intraperitoneal injection of normal saline, the second hyperlipidemic group (HCG) received an intraperitoneal injection of Triton (dissolved in distilled water). In the third, fourth and fifth groups, rats were injected i.p. with Tri-

ton followed by oral administration of 30 mg/kg of compound **7**, **8** and **9** respectively, dissolved in 6% DMSO/corn oil. The last group, bezafibrate (BFG), was also injected i.p. with Triton followed by oral administration of bezafibrate 65 mg/kg.

Blood Collection and Analysis of Serum After 18 h of treatment, animals were anaesthetized with diethyl ether and blood was collected from renal artery. The blood samples were immediately centrifuged (3000 rpm for 10 min) and the serum then used to determine the lipid profile by an enzymatic method using an automated analyzer instrument (Model Erba XL-300, Germany, Mannheim).

Statistical Analysis Results were expressed as mean values±standard error of the mean (S.E.M.). Data obtained by Graph pad PRISM software version 7.00 (2016), using Student's *t*-test, and differences with $p<0.05$ were considered statically significant, $p<0.01$ were considered as statically very significant, $p<0.001$ were considered as statically very highly significant and $p<0.0001$ were considered as statically extremely significant.

Results

Chemistry The synthesis of compounds **7**, **8** and **9** was achieved as reported in Chart 1, starting by activation reaction of benzimidazole propionic acid (**1**) with oxalyl chloride (**2**) to give the acyl derivative intermediate **3** which in turn proceeds towards a coupling reaction with the amino benzophenones **4**, **5** and **6** to give the desired compounds **7**, **8** and **9**.

Hypolipidemic Activity Novel benzimidazole-2-carboxamide derivatives **7**, **8** and **9** were tested *in vivo* for their hypolipidemic activity at a dose of 30 mg/kg body weight.

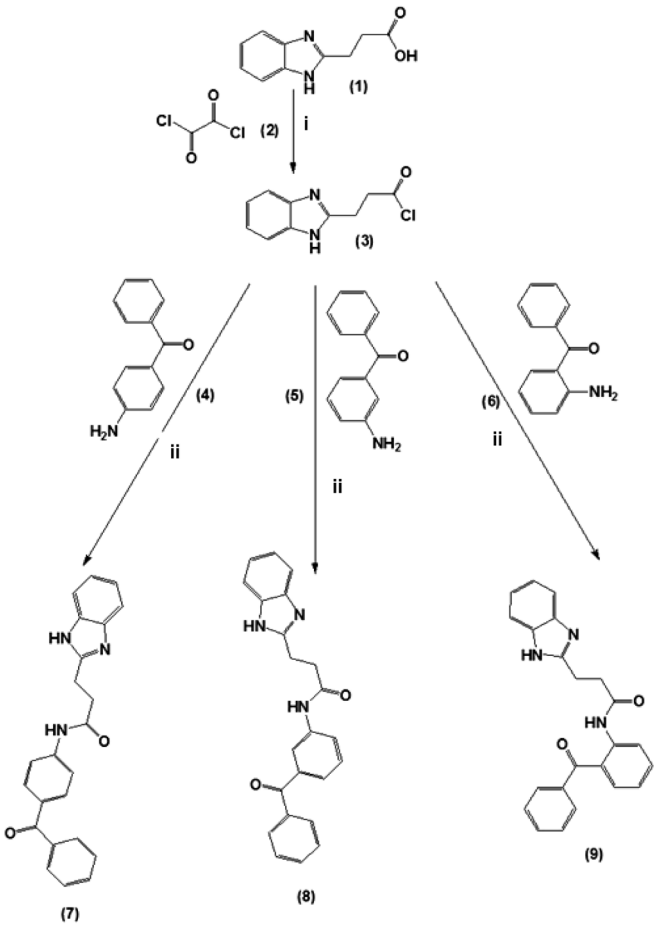
The plasma TG, HDL, LDL and TC levels for NCG, HCG, BFG, compounds **7**, **8** and **9** at 18 h after Triton administration are shown in Table 1.

Interestingly, the elevated plasma TG levels were significantly reduced by all prepared compounds, compound **7** ($p<0.0001$), compound **8** ($p<0.0001$), and compound **9** ($p<0.0001$), with a reduction percentage 93.14, 87.7 and 94.74%, respectively, compared to Bezafibrate ($p<0.0001$) with a reduction of 84.61%.

In addition, the reduced plasma HDL levels were significantly increased by all prepared compounds, compound **7** ($p<0.05$), compound **8** ($p<0.001$), and compound **9** ($p<0.05$), while bezafibrate decreased HDL levels ($p<0.001$). Furthermore, the elevated plasma LDL levels were significantly reduced by compound **8** ($p<0.001$), and compound **9** ($p<0.01$) with percentage of 54.75, 64.4%, respectively. Bezafibrate ($p<0.05$) reduced it by 49.45%. While compound **7** did not significantly decrease LDL levels ($p<0.09$) observing only 35.95% decrease. Finally, the elevated plasma TC levels were significantly reduced by all prepared compounds, compound **7** ($p<0.05$), compound **8** ($p<0.001$), and compound **9** ($p<0.001$) with a percentage of 6.6, 57.41, 87.52%, respectively. Bezafibrate ($p<0.001$) reduced it by 65.16%.

Discussion

Hyperlipidemia was produced using Triton WR-1339 *in vivo* model. All tested compounds (**7**, **8**, and **9**) were subjected to *in vivo* analysis study after 24 h of treatment. Triton WR-1339 model gave similar pattern in lipid profile changes in accordance with published work.[11–17] The tested compounds have demonstrated significant antihyperlipidemic activity. They



(i) DMF (2 drops), DCM. (ii) TEA, $CHCl_3$.

Chart 1. Synthesis of Benzimidazole Propyl Carboxamide Benzophenone Derivatives **7**, **8** and **9**

Table 1. Lipid Profile of the Tested Groups in Triton WR-1339 Induced Hyperlipidemic Rats

Groups	Lipid levels (mg/dL) after 18 h of treatment			
	TG	HDL	LDL	TC
NCG	55.5±2.4	42.7±1.7	23±1.1	88±6.2
HCG	1254±12.4*^{c}	31.4±2.1**^{c}	120±3.2*^{c}	320.5±7.5*^{c}
BFG	193 ±40**^{d}	19.85±0.35**^{c}	60.66±9.5**^{a}	112±19**^{c}
7	86±8.62**^{d}	226.77±18.04**^{a}	76.86±4.1^{ns}	299.33±4.56**^{a}
8	154±3.2**^{d}	37.3±6.9**^{c}	54.3±2.8**^{c}	136.5±4.8**^{c}
9	66.00±24.00**^{d}	37.3±18.5**^{a}	42.72±11.5**^{b}	40±32.01**^{c}

Values are expressed as means±S.E.M. from five animals in each group. *Compared to NCG group, **compared to HCG, $^{a}p<0.05$, $^{b}p<0.01$, $^{c}p<0.001$, $^{d}p<0.0001$, ^{ns}non-significant.

resulted in a statistically significant decrease in TG, LDL and TC levels and resulted also in a significant increase in HDL levels compared to hyperlipidemic group (Table 1). This biological activity can be explained by the findings in our recent study that has established the downregulation of the usually overexpressed genes in Triton WR-1339 treated rats. In fact when the animals are treated with *N*-(3-benzoylphenyl)-1*H*-indole-2-carboxamides. We observe a significant decrease in Apoc3, Apob, Acaa2, Acs11, and Slc247a5 gene expression levels which are usually overexpressed in Triton WR-1339 treated rats,[19] this result does not exclude the possibility of interactions with peroxisome proliferator-activated receptor (PPAR) alpha due to the structural similarities between the novel benzimidazole-2-carboxamide derivatives and some fibrates such as fenofibrate and bezafibrate.[20]

These excellent biological results of compounds **7**, **8**, and **9** can be explained by the presence of aromatic heterocyclic ring (benzimidazole) attached to large lipophilic aromatic rings (the benzophenone moieties) through a carboxamide ethylene linkage. These results are in agreement with previously published data.[17]

The introduction of benzimidazole instead of the previous heterocyclic aromatic rings has improved water solubility in comparison with those already reported in the literature.[11–17] This improvement could in part explain their improved biological effects. It was found that the replacement of indole or furan or thiophene nucleus by benzimidazole has produced more water soluble compounds.

This increment in water solubility can be explained by the p*K*s of the used heteroaromatic nucleus as follows: benzimidazole ring (pK_a=16.4), pK_a value of the indole=21, the furan pK_a=35.6, and thiophene pK_a=33. As a matter of a fact, during the biological testing of the indole, furan and thiophene carboxamide derivatives; compounds dissolved in water formed turbid solutions and suspensions accompanied by a precipitate even when 6% DMSO (v/v) solutions were used. On the other hand, compounds **7**, **8**, and **9** exhibited more water solubility generating clear solutions under the same conditions. Enhanced water solubility observed in compounds **7**, **8**, and **9** certainly affects positively the biological response owing to their complete dissolution reflecting their real concentrations.

Finally, it is important to highlight that carboxamide ethylene bridge linking between the benzimidazole ring and the benzophenone hydrophobic portion, which represents the second new structural feature of the new series of benzimidazole derivatives, has also positively affected their biological activity.

All novel benzimidazole carboxamide benzophenone compounds; **7**, **8**, and **9** have been found to possess a significant anti-hyperlipidemic activity. They were found to have a statistically significant decrease in TG, LDL, and TC levels after 18 h of Triton WR-1339 administration. In addition, all tested compounds resulted in a significant increase of HDL levels, which is known for its preventive role against atherogenesis, compared to hyperlipidemic group.

Conclusion

This work has introduced potent hypolipidemic new lead compounds of the benzophenone carboxamide series achieved through the preparation of benzimidazole carboxamide benzophenone derivatives (compounds **7**, **8**, and **9**). Prepared compounds were evaluated for their hypolipidemic activity using Triton WR-1339 induced hyperlipidemic rats and resulted in a statistically significant antihyperlipidemic activity, a decrease in plasma TGs, LDL, and TC levels. In addition to the significant increase in high-density lipoprotein HDL levels after 18 h of treatment. The results of this study are highly promising and structural optimization and further investigations are running to explore their exact mechanism of action and to develop more potent derivatives.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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