PAPER

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Trapping of thermally generated *ortho*- and *para*-quinone methides by imidazoles and pyrazoles: a simple route to green synthesis of benzopyrone-azole hybrids and their evaluation as α-glucosidase inhibitors†

Andrii S. Myshko, [ID] ab Galyna P. Mrug, [ID] a Svitlana P. Bondarenko, [ID] c Kostyantyn M. Kondratyuk, [ID] a Oleksandr L. Kobzar, [ID] a Vladyslav M. Buldenko, [ID] a Andriy V. Kozytskiy, bd Andriy I. Vovk [ID] a and Mykhaylo S. Frasinyuk [ID] ★ab

An efficient green approach for the trapping of *in situ* generated *ortho*-and *para*-quinone methide intermediates by imidazoles and pyrazoles has been developed. A wide range of quinone methide precursors based on simple phenols are compatible with the experimental protocol under mild thermal conditions. This methodology was demonstrated to be suitable for the synthesis of methylene-linked benzopyrone-azole hybrids using naturally occurring coumarin and chromone Mannich bases. In most cases, the products were isolated in good to excellent yields without chromatographic purification. *In vitro* studies showed that some of the synthesized compounds exhibit inhibitory activity towards α-glucosidase.

Introduction

Chemical properties of five-membered nitrogen-containing heterocycles with two or more heteroatoms commonly named "azoles" depend on the number, nature, and positions of heteroatoms in their skeleton. Among them, imidazoles and pyrazoles with isomeric ring systems containing two nitrogen atoms show the most distinct amphoteric properties, which make it possible to afford a wide range of derivatives using various reactions. The importance of these aromatic ring systems is reflected by their presence in naturally occurring histidine, histamine, purines, and several classes of pharmaceuticals. Recent advances in the synthesis and biological activity of compounds based on these heterocyclic cores are discussed in chapters of a monography[1] and a book[2] as well as references cited herein.

A common and widely used method for the *N*-alkylation of azoles includes the action of alkyl halides, pseudo halides, or sulfates with azole metal salts or azoles in the presence of a strong base. However, applying these procedures for the synthesis of target compounds bearing phenolic fragments requires the protection of at least the phenolic groups.

On the other hand, the reaction of phenols, azoles, and formaldehyde can be considered as a Mannich reaction whereas azoles play the role of the amino component. Probably due to low nucleophilicity of azoles, the application of only imidazole with simple phenols was reported in the literature,[3] and other azoles could be involved in the reaction using 2-naphthol as a very active CH-component.[4] However, direct imidazolylmethylation of simple phenols has limitations due to the possible formation of bis-imidazolylmethyl phenols[3d] or the formation of methylene-bis-phenols.[3c]

Natural compounds have played a significant role as sources of new drugs over nearly four decades.[5] Among them, flavonoids and coumarins are recognized as privileged scaffolds in medicinal chemistry.[6] In the framework of benzopyrone-azole hybrids, imidazolylmethylflavones were identified as aromatase inhibitors,[7] inhibitors of corticosteroid biosynthesis,[8] and antiproliferative agents,[9] whereas various 2-azolylmethylchromones were studied as kinase modulators.[10] Their synthetic protocols were developed by using the intermediate halomethyl derivatives of benzopyrones and subsequent reaction with azoles. Protection of phenolic groups was required for the obtaining of target hydroxylated derivatives.

Quinone methides with general structures **1** (Fig. 1) are highly polarized and hence reactive under nucleophilic and electrophilic conditions.

ᵃV. P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, NAS of Ukraine, 1 Academician Kukhar Str., Kyiv 02094, Ukraine. E-mail: mykhaylo.frasinyuk@ukr.net
ᵇEnamine Ltd., 78 Winston Churchill Str., Kyiv 02094, Ukraine
ᶜNational University of Food Technologies, Kyiv 01601, Ukraine
ᵈChemBioCenter, Taras Shevchenko National University of Kyiv, 64 Volodymyrska Str., Kyiv 01601, Ukraine
† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4ra05230g
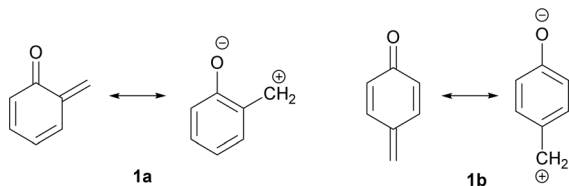
Fig. 1 Structural features of *ortho*- and *para*-quinone methides.

A few attempts were reported for the synthesis of imidazolylmethylphenols *via* Michael's addition of imidazole to *in situ*-generated quinone methides. This route was used for the synthesis of 1*H*-5-hydroxybenzimidazole,[11] 6-hydroxyquinoline,[12] and 5-hydroxyindole[13] derivatives with anti-hepatitis activity, as well as for modification of camptothecin[14] for the design of topoisomerase I inhibitors (Fig. 2).

Considering the obvious multiple advantages of applying quinone methides in the context of the development of synthetic procedures, we embarked on a study of the feasibility of these intermediates for the conjugation with azaheterocycles in environmentally benign conditions. Herein, we report the realization of this goal; specifically, we describe using dimethyl carbonate for the generation of *ortho*- and *para*-quinone methides followed by their trapping by azoles. This protocol proved to be effective for using different quinone methide precursors based on simple phenols and naturally occurring benzopyrones.
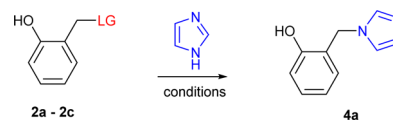
Results and discussion

Synthetic and commercial availability of quinone methide precursors could facilitate the development of the conjugation protocols of phenols and azoles. Using them has some lacks

and advantages and choosing each should be appreciated in a strategy of the synthesis. As *ortho*-quinone methide precursors, *ortho*-dimethylaminomethylphenols are easily accessible using Mannich reaction contrary to *para*-dimethylaminophenols which can be synthesized by reductive amination often with poor yield. Both precursors such as 2-hydroxymethylphenols and 4-hydroxymethylphenols can be synthesized by the reduction of numerous commercially available substituted hydroxylated aldehydes, but their use for the synthesis of azolylmethylphenols requires high temperatures.[15] Moreover, using 2- or 4-methoxymethylphenols requires additional steps for their synthesis, but has an advantage in the case of catechols[16] or the synthesis derivatives from natural phenolic compounds bearing methoxymethyl group.[17]

As a model reaction for the construction of benzopyrone-azole hybrids, we chose a reaction of *ortho*- and *para*-substituted phenols bearing dimethylaminomethyl, hydroxymethyl, or methoxymethyl groups **2a–2c** and **3a–3c** as possible precursors[18] for generation of quinone methides with subsequent trapping them with imidazole, pyrazole, and related benzimidazole or 3,5-dimethylpyrazole (as analogs with low nucleophilicity). However, the reported procedure for the capture by azoles of quinone methides in aqueous conditions[19] was not applicable for benzopyrone derivatives due to their poor solubility.

Fig. 2 Biologically active compounds synthesized by Michael's addition of imidazoles/adenine to *in situ*-generated quinone methides.

Table 1 Development and optimization for the synthesis of compound **4a**[a]

Compd. (LG)	Solvent	Temp., C	Conversion[b], %	Purity[c], %
2a (NMe₂)	EtOH	80	n.r.	—
2a (NMe₂)	(MeO)₂CO	90	83	85
2a (NMe₂)	1,4-Dioxane	100	53	78
2a (NMe₂)	Toluene	110	50	85
2a (NMe₂)	(EtO)₂CO	126	78	82
2a (NMe₂)	DMF	154	72	78
2b (OH)	EtOH	80	n.r.	—
2b (OH)	(MeO)₂CO	90	43	91
2b (OH)	1,4-Dioxane	100	39	89
2b (OH)	Toluene	110	35	90
2b (OH)	(EtO)₂CO	126	38	93
2b (OH)	DMF	154	53	86
2c (OMe)	EtOH	80	n.r.	—
2c (OMe)	(MeO)₂CO	90	73	92
2c (OMe)	1,4-Dioxane	100	45	83
2c (OMe)	Toluene	110	48	85
2c (OMe)	(EtO)₂CO	126	69	90
2c (OMe)	DMF	154	67	75

[a] A mixture of quinone methide precursors **2a–2c** (2 mmol) and imidazole (4 mmol) in an appropriate solvent (5 mL) was refluxed for 24 h. [b] Was determinate by LCMS spectra. [c] Calculated by LCMS spectra excluding intact reagents.
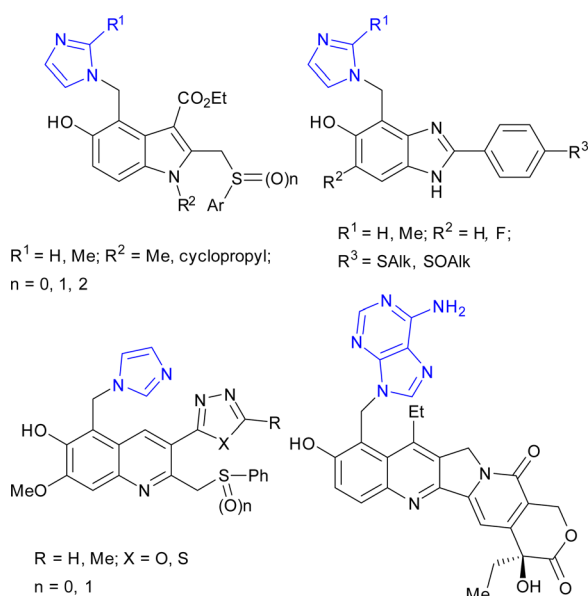
In the first stage, to determine the role of solvents and temperature, we investigated the reaction of *ortho*-substituted phenol **2a–2c** with imidazole at various conditions (Table 1). According to these data, dimethyl carbonate (DMC) was chosen as the most acceptable solvent for further development of phenol–azole conjugate synthesis. However, these data were insufficient for elucidation of the most useful leaving group (LG) for the reaction with other azoles, especially in cases of using naturally occurring compound derivatives. Our next experiments were focused on further optimization of the reaction conditions of compounds **2** and **3** with some azoles.

Phenol-methylene azoles **4** and **5** were synthesized by refluxing compounds **2a–2c** and **3a–3c** with [benz]imidazole and pyrazoles in dimethyl carbonate for 36 h.
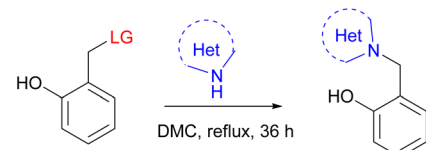
Using 2-dimethylaminomethylphenole **2a** was successful for the synthesis of imidazoles **4a, 5a** and benzimidazoles **4b, 5b**. In the cases of 2- and 4-hydroxybenzylphenols **2b, 3a,** and **3c**, the target hybrids were synthesized with acceptable to good yield with all azoles. However, the addition of acids such as trifluoroacetic or methane sulfonic was needed to complete the reactions. It should be noted that the reaction of 2-hydroxymethylphenol with imidazole requires high temperature.[15a] The reactions of imidazole or benzimidazole with 2-methoxymethylphenol **2c** and 4-methoxymethylphenol **3b** were

completed in 24 h whereas conversion of these methoxymethyl derivatives with pyrazole or 3,5-dimethylpyrazole was approximately 40% and was not completed after 72 h.
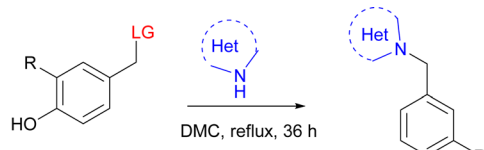
Thus, imidazole derivatives **4a, 5a,** and **5e** can be synthesized from all precursors with poor to good yield, whereas applying hydroxymethylphenols **2b, 3a,** and **3c** was more suitable for the synthesis of benzimidazole derivatives **4b, 5b,** and **5f**. The more effective conditions for the synthesis of related pyrazole and 3,5-dimethylpyrazole derivatives were achieved using hydroxymethyl phenols **2b, 3a,** and **3c** in the presence of acids (Table 2).

Our findings were extended to the application of [benz]imidazole and pyrazoles for the synthesis of azole-phenol hybrids bearing a coumarin or chromone fragment, as attractive compounds which represented naturally occurring bioactive phenols. Thus, umbelliferone (7-hydroxycoumarin, **6a**), 4-methylumbelliferone (**6b**), 2,3-dimethylchromone (**6c**), soybean isoflavonoids daidzein (7,4′-dihydroxyisoflavone, **6d**), formononetin (7-hydroxy-4′-methoxyisoflavone, **6e**), cladrin (7-hydroxy-3′,4′-dimethoxyisoflavone, **6f**), pseudobaptigenin (7-hydroxy-3′,4-methylenedioxyisoflavone, **6g**), 2-methyl-formononetin (**6h**), their fluorinated derivatives 2-trifluoroformononetin (**6i**) and 7-hydroxy-4′-
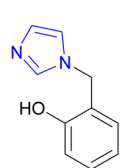

Table 2 Scope of substrates in the reaction of phenol derivatives with azoles[a]
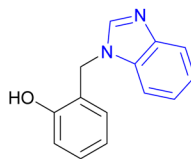
2a, LG = NMe₂
2b, LG = OH [b]
2c, LG = OMe
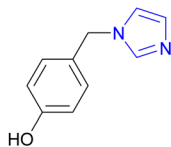
3a, R = H, LG = OH [b]
3b, R = H, LG = OMe
3c, R = OMe, LG = OH [b]

4a - 4d

5a - 5h
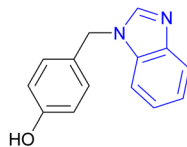
4a, 73% (from **2a**)
70% (from **2b**)
59% (from **2c**)
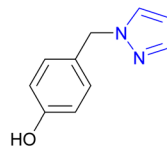
4b, 39% (from **2a**)
43% (from **2b**)
35% (from **2c**)

5a, 49% (from **3a**)
36% (from **3b**)

5b, 53% (from **3a**)
38% (from **3b**)

5c, 55% (from **3a**)
58% (from **3b**)

5d, 43% (from **3a**)
39% (from **3b**)

4c, 52% (from **2b**)
48% (from **2c**)
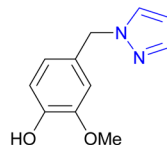
4d, 56% (from **2b**)
58% (from **2c**)
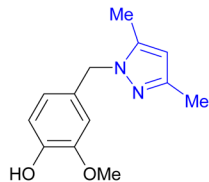
5e, 79%

5f, 53%

5g, 76%

5h, 54%

[a] Isolated yield. [b] In the presence of 10 mol% of CF₃COOH.

Table 3 Scope of substrates in the reaction of benzopyrone derivatives with azoles

9a, R= H, 73%
9b, R = Me, 94%

9d, R = H, 73% [a]
9j, R = CF$_3$, 85%

9e, R = H, 82%
9h, R = Me, 83%
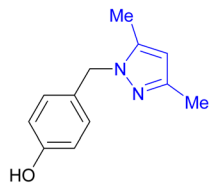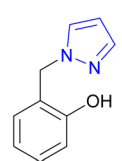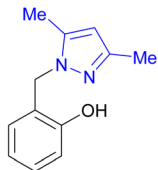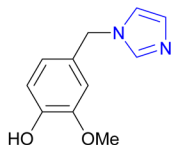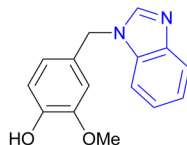**9i**, R = CF$_3$, 86%

9f, R^1= R^2 = Me, 92%
9g, R^{1}R^2 = CH$_2$, 86%

9c (imidazole), 91%
10c (benzimidazole), 70%

10a, R=H, 75%
10b, R = Me, 69%

10d, R= H, 71%
10f, R = Me, 72%
10g, R = CF$_3$, 81%

10e, 89%

10h, 79%

11a, R^1=R^2= H, 73%
11b, R^1= Me, R^2= H, 68%
12a, R^1= H, R^2= Me, 79%

11d, R^1 = R^2 = H, 81% [a]
11j, R^1 = CF$_3$, R^2 = H, 90%
12c, R^1 = H, R^2 = Me, 72% [a]
12i, R^1 = CF$_3$, R^2 = Me, 81%

11e, R= H, 80%
12d, R = Me, 76%

11f, R= H, 93%
12e, R = Me, 72%

11g, R= H, 83%
12f, R = Me, 75%

11c, R = H, 65%
12b, R = Me, 69%

11h, R= H, 72%
12g, R = Me, 77%

11i, R= H, 67%
12h, R = Me, 80%

[a] Reaction was performed in 1.4-dioxane.

trifluoromethoxyisoflavone (**6j**) were used for the synthesis of hybrids with the mentioned azoles.

Taking into account that the efficiency for the generation of *ortho*-quinone methides **7a–7j** with fused pyrone ring from complex compounds can be significantly different from simple phenol derivatives **2** or **3**, we carried out the reaction of 8-

substituted formononetin derivatives with imidazole. As a result, target formononetin-imidazole hybrid **9e** was isolated from reaction imidazole with 8-dimethylaminomethylformononetin **8e**, (82% yield, 100% purity), 8-hydroxymetylformononetin[20] (78% yield, 95% purity), and 8-methoxymethylformononetin[20] (84% yield, 95% purity).
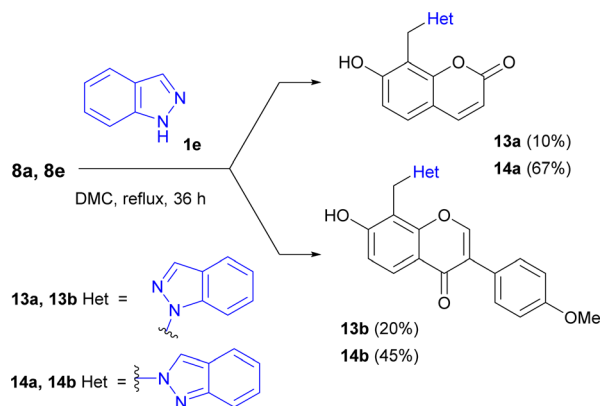
Scheme 1   Synthesis of indazole-benzopyrone hybrids **13** and **14**.

Fig. 3   Key correlations for determination of structures **13** and **14**.

Table 4   Inhibition of α-glucosidase by synthesized benzopyrone-azaheterocycle hybrids[a]

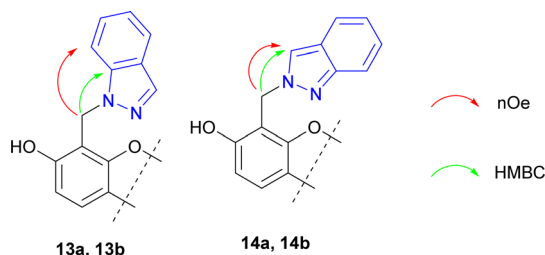| Compound	Inhibition at 25 μM (%)	IC$_{50}$, μM
9b	53.4	23.6 ± 1.8
9d	42.0	27.0 ± 0.2
9i	73.7	20.0 ± 2.0
10b	69.3	21.1 ± 0.7
10d	64.6	20.6 ± 2.1
10f	48.6	25.5 ± 7.9
10g	79.6	15.9 ± 4.7
10h	99.1	9.5 ± 1.6
11d	62.5	16.2 ± 3.4
11j	84.1	14.3 ± 2.0
12c	42.8	27.4 ± 1.9
12d	67.3	20.9 ± 2.5
12h	66.9	21.2 ± 0.7
12i	94.0	5.8 ± 0.2
13b	73.0	17.1 ± 2.8
14b	50.3	23.9 ± 2.3
Acarbose[b]		760.6 ± 120.3

[a] IC$_{50}$ values are shown as average value $\pm$ standard deviation. [b] Reference compound.

According to these data and synthetic availability of 7-hydroxycoumarin or 7-hydroxychromone derivatives for the generation of *ortho*-quinone methides, we used their 8-dimethylaminomethyl derivatives **8a–8j** in reaction with azoles in dimethyl carbonate at reflux. As a result, a series of coumarin- and

chromone-azole hybrids were synthesized with good to excellent yield and 95–99% purity at the reflux of Mannich bases **8a–8c** and **8e–8j** with 2-fold excess of azoles in dimethyl carbonate. However, using of 1,4-dioxane was needed in the case of daidzein Mannich base **8d** due to its poor solubility in dimethyl carbonate and the formation of by-pass products (Table 3).

The reaction of 7-hydroxycoumarin or formononetin Mannich bases **8a**, **8e** with indazole led to the formation of both possible isomers, 8-(1-indazolylmethyl)-7-hydroxybenzopyrones **13a**, **13b** and 8-(2-indazolylmethyl)-7-hydroxybenzopyrones **14a**, **14b** (Scheme 1) with excess of compounds **14**.

The structures of synthesized compounds **13** and **14** were elucidated using 1D NOESY, HSQC, and HMBS techniques (Fig. 3).

We presume that using asymmetrical azoles should afford mixture of both possible N-alkylated regioisomers in the ratio, which can depend on various factors, mainly steric hindrance of substituents and reaction time. In our opinion, a steric hindrance determines the key role, which was demonstrated by indazole use.

The naturally occurring flavonoids, their derivatives, and related compounds are widely studied as α-glucosidase inhibitors.[21] The various synthetic heterocycle-containing coumarins and chromones were identified as promising inhibitors of this enzyme.[22] In the case of isoflavone derivatives, a substituent at position 8 can influence their inhibitory potency.[23] Among the compounds synthesized in this study, the sixteen benzopyrone-azaheterocycle hybrids inhibited α-glucosidase activity by 42–99% at the concentration of 25 μM. The determined IC$_{50}$ values were in the range of 5.8 μM to 27.4 μM (Table 4). The 4′-trifluoromethoxy derivatives **10h** and **12i** bearing 1-benzimidazolylmethyl or 3,5-dimethyl-1-pyrazolylmethyl groups at position 8 of the isoflavonoid skeleton were found to be the most effective inhibitors with IC$_{50}$ values of 9.5 μM and 5.8 μM, respectively. At the same time, 8 non-substituted 4′-trifluoromethoxy isoflavonoid **6j** exhibited much lower inhibitory activity (39% at 25 μM) against this enzyme.

Conclusions

In summary, we have demonstrated that *ortho*- and *para*-quinone methides can be efficiently generated under thermal conditions in dimethyl carbonate. In contrast to most known methodologies, this protocol allows using water-insoluble compounds and does not require the use of high temperatures and harmful solvents. Various precursors for the generation of quinone methides showed high efficiency in trapping these intermediates by azoles. Also, coumarin and chromone Mannich bases were used for the synthesis of benzopyrone-azole hybrids in good to excellent yield which makes our protocol well-suited for large-scale syntheses. Our protocol could also be implemented for the generation and trapping of *ortho*-quinone methide intermediates from various naturally occurring 2-hydroxymethyl- or 2-methoxymethylphenols. Several of the synthesized methylene-linked benzopyrone-azaheterocycle hybrids were found to be α-glucosidase inhibitors with IC$_{50}$ values of 5.8–27.4 μM.

Experimental

Chemistry

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker AVANCE DRX 500 (500/125/470 MHz) or AVANCE III 400 (400/100/376 MHz) spectrometers in CDCl$_3$ [residual CHCl$_3$ ($\delta_H = 7.26$ ppm) or CDCl$_3$ ($\delta_C = 77.16$ ppm) as internal standard] or DMSO-d_6 [residual SO(CD$_3$)(CD$_2$H) ($\delta_H = 2.50$ ppm) or SO(CD$_3$)$_2$ ($\delta_C = 39.52$ ppm) as internal standard]. 2D NMR spectra were recorded on Agilent ProPulse 600 MHz. Melting points were determined in open capillary tubes using the Buchi B-535 apparatus and were uncorrected. IR spectra were recorded on a Bruker Vertex 70. Mass spectra were obtained using an Agilent 1100 spectrometer using APCI (atmospheric-pressure chemical ionization). Elemental analysis was performed on a vario MICRO cube automated CHNS-analyzer. Column chromatography was performed using Macherey-Nagel Silica 60, 0.04–0.063 mm silica gel.

Synthesis of Mannich bases **8a**,[24] **8b**,[25] **8e–8i** (ref. 26) was described previously. Inhibition of α-glucosidase by compounds **4–5** and **9–14**, characteristics of synthesized compounds, and copies of their NMR spectra are provided in ESI†.

General procedure for the synthesis of compounds 4 and 5. A mixture of appropriate compounds **2a–2c**, **3a–3c** (1 mmol), azole **1a–1d** (2 mmol) in the presence of 0.025 mL of trifluoroacetic or methanesulfonic acid (in case of compounds **2b**, **3a**, or **3c**) in 5 mL of dimethyl carbonate was refluxed for 36 h. The reaction mixture was cooled, evaporated, diluted with 20 mL of water, and filtered off. The solid was purified by recrystallization from the ethanol–water mixture.

7-Hydroxy-3-[4-(trifluoromethoxy)phenyl]-4H-chromen-4-one (**7j**) was synthesized according to typical procedure.[27]

General procedure for the synthesis of Mannich bases 8c, 8d, and 8i. To a stirred suspension of isoflavonoids **6c**, **6d**, or **6j** (2 mmol) in 10 mL of isopropanol was added 0.3 mL (2.2 mmol, 1.1 eq) of bis(N,N-dimethylamino)methane at 70 °C. The mixture was heated at 80 °C for 2 h and cooled to afford a precipitate that was collected by gravity filtration. The Mannich bases **8** were re-crystallized from isopropanol-hexane.

General procedure for the synthesis of benzopyrone-azole hybrids 9–12. A mixture of benzopyrone Mannich base **8a–8j** (1 mmol) and azole **1a–1d** (2 mmol) in 5 mL of dimethyl carbonate (or 1,4-dioxane in case of compound **8d**) was refluxed for 36 h. The reaction mixture was cooled, diluted with 10 mL of ethanol, and filtered off. The solid was purified by recrystallization from ethanol.

Synthesis of indazole derivatives **13** and **14** was carried out similarly to the general procedure. The mixture of isomeric indazole derivatives was separated by column chromatography using 100 : 1 CH$_2$Cl$_2$–MeOH (for compounds **13a** and **14a**) or ethyl acetate (for compounds **13b** and **14b**).

Biology

α-Glucosidase from *Saccharomyces cerevisiae* and *p*-nitrophenyl α-D-glucoside as a substrate were purchased from Sigma-Aldrich.

In vitro α-glucosidase inhibition study. The reaction volume (2.0 mL) consisted of 57 mM sodium phosphate buffer (pH 6.8), 1% dimethyl sulfoxide (DMSO), 0.85 mM substrate, inhibitor, and enzyme. Firstly, the reaction mixture, which included buffer, DMSO, inhibitor, and enzyme, was incubated at 37 °C for 5 min. Then, the enzymatic reaction was started by the addition of *p*-nitrophenyl α-D-glucopyranoside. The activity of α-glucosidase was monitored spectrophotometrically at 400 nm. The inhibition percentage was determined using the equation:

$$\% \text{ inhibition} = 100 - ((A_{\text{sample}} \times 100)/A_{\text{control}})$$

The IC$_{50}$ values were determined from dose-dependent curves using semi-logarithmic plots (percentage of remaining α-glucosidase activity *versus* logarithm of inhibitor concentration) and linear trend equations. The dose-dependent curve for each of the compounds was obtained from the results of 2–3 experiments, which included the determination of the remaining activity of α-glucosidase at several inhibitor concentrations.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Conceptualization, A. I. Vovk, M. S. Frasinyuk, O. L. Kobzar; synthesis of compounds, A. S. Myshko, G. P., Mrug, S. P. Bondarenko, K. M. Kondratyuk; elucidation of structures, A. Kozytskiy; biological assays, V. M. Buldenko, O. L. Kobzar; writing – review and editing, M. S. Frasinyuk, O. L. Kobzar, A. I. Vovk.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

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