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Novel sulfonamide-functionalized arylidene indolones as potent α-glucosidase inhibitors: synthesis, characterization, and *in vitro* and *in silico* studies

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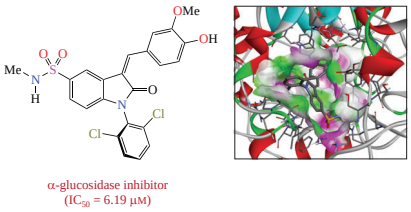
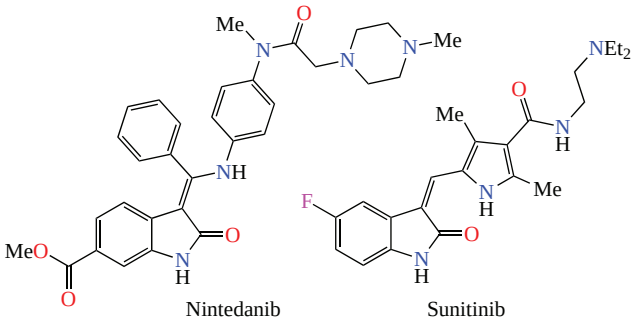
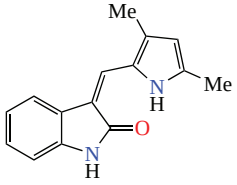
3-Arylidene-1-(2,6-dichlorophenyl)indolones and in particular their 5-methylaminosulfonyl derivatives efficiently inhibit α-glucosidase enzyme. The results are corroborated by *in silico* docking studies which show the binding of aminosulfonyl derivatives to be more favorable due to additional hydrogen bonding. The most active compound of the series shows the IC_{50} of 6.19 μM.



Keywords: indolones, arylidene indolones, sulfonamides, α-glucosidase inhibitor, enzyme docking.

Indole and indolone scaffolds common in alkaloid natural products[1] have been of great interest for their biological activity. Their derivatives demonstrate antimicrobial,[2] antiviral,[3] anticonvulsant,[4] and anti-tumor activity.[5–7] Examples include an angiokinase inhibitor and an effective antiproliferative drug (Nintedanib), as well as a tyrosine kinase inhibitor used for treatment of gastrointestinal stromal tumors (Sunitinib). Semaxanib, although failed in phase III clinical trials, has been a tyrosine kinase inhibitor for colorectal cancer treatment. It is interesting to notice that these and some other compounds with strong biological activities belong to C^3=C-substituted indolone chemotype. Such compounds are readily available from base-catalyzed reactions between indolones and aldehydes.[8] The simplicity of the synthetic procedure and the diversity of aldehyde counterparts allow easy preparation of a large library of C^3-substituted alkylidiene/arylidene indolones for biological activity investigation.

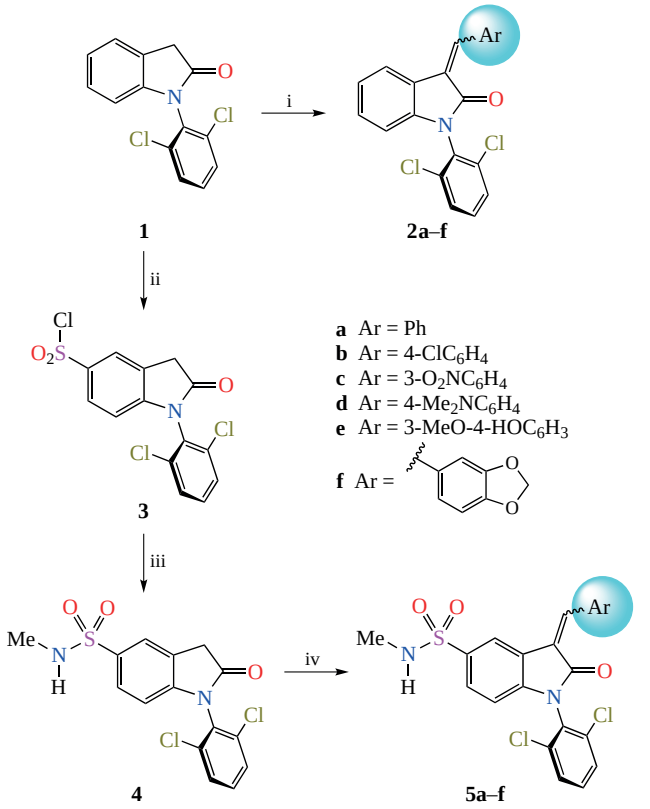




In parallel, sulfonamide is one of many pharmacophores widely accepted in clinical usage. Sulfonamide-functionalized compounds have demonstrated a wide range of biological activities, *i.e.* enzyme inhibitions,[9] and antidiabetic,[10] antimicrobial,[11] anticancer, antiparasitic, and antioxidant properties.[12–14]

Despite the success of the two scaffolds, it is interesting to notice that there are only a few works exploring the synthesis and potential application of sulfonamide-functionalized arylidene indolones. Sulfonamide isatin displayed nanomolar potency for inhibiting the executioner caspases 3/7[15] while 3-hydroxy-2-oxoindole derivatives bearing the sulfonamide group were highly active antiviral agents.[16] Nonetheless, their activities toward α-glucosidase enzyme, a target for type 2 diabete treatment, were not fully explored. We herein report on synthesis and α-glucosidase inhibition activities of a series of sulfonamide-functionalized arylidene indolones bearing a biologically relevant 2,6-dichlorophenyl *N*-substituent. In addition, the corresponding sulfonamide-deprived indolones were compared in relation of biological activity, although some of them were the known compounds.[17]

The synthesis of 3-arylidene-1-(2,6-dichlorophenyl)-2-oxo-indolines **2a–f** and 3-arylidene-1-(2,6-dichlorophenyl)-5-methylaminosulfonyl-2-oxoindolines **5a–f** is outlined in Scheme 1. The starting 1-(2,6-dichlorophenyl)-2-oxoindoline **1** was synthesized using an efficient, practical, environmentally benign, and high yielding one step reaction. The sulfonamide-free derivatives **2a–f** were obtained in good yields by piperazine-catalyzed aldol condensation between **1** (involving the 3-positioned CH-acidic methylene group) and a series of benzaldehydes.[18] In parallel, the hydrogen atom at C^5 in compound **1** was substituted by the chlorosulfonyl group. This electrophilic substitution reaction with chlorosulfonic acid occurred regioselectively due to the *para*-directionality of the N–CO group to furnish product **3** in 98% yield, which did not



Scheme 1 *Reagents and conditions*: i, RCHO, piperazine, EtOH, 80 °C; ii, $ClSO_3H$, 0 → 20 °C; iii, $MeNH_2$, CH_2Cl_2; iv, RCHO, piperazine, EtOH, 80 °C.

require complicated purification. Compound **3** was easily converted into sulfonamide indolone **4** (90% yield) on treatment with methylamine. Finally, compound **4** was converted into products **5a**–**f** employing aldol condensation with the corresponding benzaldehydes. The ^{1}H NMR spectra of sulfonamide-containing arylidene indolones **5a**–**f** show peaks for C^3=C*H* (singlet), C^4*H* (singlet) above 8.00 ppm, SO_2N*H* sulfonamide (broad singlet, ~4–5.00 ppm), and NCH_3 (singlet, ~3.00 ppm). Note that the ^{1}H NMR spectra indicate that compounds **5c**,**e**,**f** were isolated as *E*–*Z* mixtures with *E*/*Z* molar ratios of 1 : 1, 2 : 1, and 1.3 : 1, respectively.

The molecular structure of **5f** was unambiguously confirmed by single crystal X-ray diffraction† (Figure 1, the single crystals were obtained by slow evaporation of its solution in a chloroform/hexane mixture). The dichlorophenyl ring is nearly perpendicular to the oxoindole core (dihedral angle of 71.5°). The arylidene ring is slightly twisted from indolone forming the dihedral angle

† *Crystal data for* **5f**. $C_{23}H_{16}Cl_2N_2O_5S$ (M = 503.34), monoclinic, space group $P2_1/c$, at 298 K: a = 17.9063(7), b = 17.1830(7) and c = 7.1177(3) Å, α = 90°, β = 92.935°, γ = 90°, V = 2187.13(15) Å^3, Z = 4, d_{calc} = 1.529 g cm^{-3}, μ(MoK$_\alpha$) = 11.42 cm^{-1} F(000) = 1032. A total of 33407 reflections were collected (5318 independent reflections, R_{int} = 0.0458) and used in the refinement, which converged to wR_2 = 0.198 and GOOF = 1.095 for all independent reflections [R_1 = 0.073 was calculated for 5318 reflections with $I > 2\sigma(I)$]. Single-crystal X-ray diffraction was collected with a Bruker D8 QUEST instrument at 298 K (MoK$_\alpha$ radiation, λ = 0.71073 Å, TRIUMPH monochromator). Collection, editing of data, and refinement of the unit cell parameters was performed using APEX2.[26] Absorption correction was performed by the multi-scan method implemented in SADABS.[27] All calculations were performed using SHELXT[28] and OLEX2 programs.[29] The structure was solved by the direct method and refinement by the least squares method in the anisotropic approximation for the non-hydrogen atoms.

CCDC 2192055 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

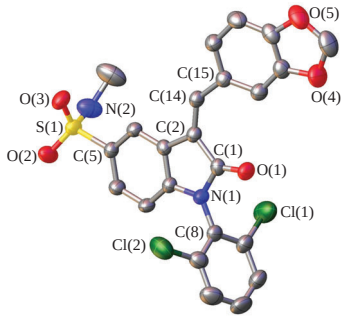


Figure 1 Solid state molecular structure of **5f**. Structural parameters: bond lengths (Å): C(1)–O(1), 1.210(4); C(1)–C(2), 1.480(4); C(1)–N(1), 1.407(4); C(4)–N(1), 1.395(4); N(1)–C(8), 1.412(4); C(2)–C(14), 1.357(4); C(3)–C(4), 1.398(4); bond angles (°): O(1)–C(1)–C(2), 132.5(3); O(1)–C(1)–N(1), 121.2(3); C(1)–C(2)–C(14), 131.0(3).

of 14.26°. The bond distances and angles are in the normal range.[19]

Type 2 diabete is accounted for almost 90–95% of diabete patients,[20] which can lead to a severe health risk including kidney disease, retinopathy, and cardiovascular disease. Inhibition of α-glucosidase activity is closely related to the treatment of the disease. Interestingly, our tests show that compounds **2a**–**f** and **5a**–**f** are good to moderate α-glucosidase inhibitors. The IC_{50} inhibition concentrations of **2a**–**f**, **5a**–**f**, acarbose, and related compounds were summarized in Table 1. Their activities were compared with the activity of acarbose (IC_{50} = 257 μM), a commercially available drug. It appears that the arylidene rings have significant influence on the activities of the compounds. Compounds bearing poor/non-hydrogen bonding benzyl (**2a**, **5a**) and 4-dimethylaminobenzyl substituents (**2d**, **5d**) are among the ones with the lowest activities. Interestingly, the α-glucosidase inhibitory activity of sulfonamide-functionalized arylidene indolones **5** are superior to the non-functionalized ones **2**, showing an enhance in activities from 1.5 to 10 times. The most active indolone is the sulfonamide derivative bearing a 4-hydroxy-3-methoxybenzyl substituent, exhibiting an IC_{50} value of 6.19 μM. Note that, to this day, few indole/indolone,[22,23] and merely any arylidene indoles[24] are shown to have α-glucosidase inhibition activity. We are not aware of any report on α-glucosidase inhibitory activities of sulfonamide arylidene indolones. Our incorporation of the sulfonamide moieties is unprecedented and yielded promising α-glucosidase inhibitors. Indeed, reactivities of the compounds are superior compared to the related 3-benzylidene-6-chloroindolin-2-one (IC_{50} 195.59 ± 0.05 μM) and 6-chloro-3-(4-dimethylaminobenzylidene)indolin-2-one (IC_{50} 91.22 ± 0.01 μM).[21]

Ligand protein docking was carried out to gain insight into the interaction between the target compounds **2a**–**f** and **5a**–**f** and α-glucosidase enzyme. The structure of α-glucosidase enzyme was obtained from protein database (PDB ID 3A4A).[25] Both the

Table 1 α-Glucosidase inhibitory of **2a**–**f** and **5a**–**f** (μM).

Compound	IC_{50}	Compound	IC_{50}
2a	74.68 ± 4.91	**5a**	53.88 ± 3.70
2b	48.72 ± 0.52	**5b**	13.44 ± 0.51
2c	65.05 ± 4.89	**5c**	10.98 ± 0.61
2d	61.42 ± 3.66	**5d**	34.91 ± 1.00
2e	77.62 ± 2.50	**5e**	6.19 ± 0.40
2f	78.00 ± 3.92	**5f**	12.26 ± 0.99
Acarbose			257 ± 6.97
3-Benzylidene-6-chloroindolin-2-one			195.59 ± 0.05[a]
6-Chloro-3-(4-dimethylaminobenzylidene)indolin-2-one			91.22 ± 0.01[a]

[a] Ref. 21.

Table 2 Binding energy and primary interactions between **2a–f** and **5a–f** and α-glucosidase.

Compound	*E*/kcal mol^{-1} (*Z*/*E*)	Compound	*E*/kcal mol^{-1} (*Z*/*E*)
2a	–9.8/–9.6	**5a**	–10.3/–10.2
2b	–10.0/–9.7	**5b**	–10.2/–9.40
2c	–10.5/–10.3	**5c**	–10.9/–10.0
2d	–9.9/–8.5	**5d**	–9.8/–9.4
2e	–9.9/–9.7	**5e**	–10.9/–10.1
2f	–10.8/–10.6	**5f**	–10.9/–10.2

Z and *E* isomers of the compounds were screened for interaction (Table 2).

The results show that the binding energies between the compounds and the active site of α-glucosidase are in the 8.5–10.9 kcal mol^{-1} range (see Online Supplementary Materials, Figure S25). It appears that the *Z* configuration of all compounds is slightly more energetically favorable. A representative comparison of interaction between *Z*-**5e** and *E*-**5e** to the protein is presented in Figure 2. Note that the sulfonamide derivatives **5** bind more strongly than their analogs **2**. In general, non-sulfonamide indolones **2a–f** interact with the protein pocket mainly *via* van der Waals interactions, except for **2c** and **2e**, where one hydrogen bond is formed with substituent –NO_2 and –OMe (see Online Supplementary Materials, Tables S1–S3). On the other hand, compounds **5a–f** all interact with the binding pocket *via* arene–cation interaction with the residue Arg-315, arene-anion interaction with Asp-307 and π–π stacking with His-280. There is also a hydrogen bond between C=O of the indolone ring and His-280. The sulfonamide group in **5d** only forms one hydrogen bond with Agr-442 (bond length: 2.24 Å). More importantly, the sulfonamide group in compounds **5a–f** with a high binding energy also provides more contact with the pocket *via* two more hydrogen bonds with the residue Ser-157 (bond length: 2.33–2.37 Å), and Lys-156 (bond length: 2.69–2.76 Å) (Tables S4–S6).

In summary, a series of six arylidene indolones **2a–f**, and six novel sulfonamide arylidene indolones **5a–f** have been successfully synthesized. *In vitro* tests show that they can serve as moderate-to-good α-glucosidase inhibitors displaying an IC_{50} concentration in the range of 6.19 to 78.00 μM. Especially, the incorporation of the sulfonamide group at C^5 position of the indolone moiety improves the inhibitory activity. The difference in reactivity is rationalized by a molecular docking study, which suggests additional hydrogen bonding offered by the sulfonamide group to protein, leading to more energetically favorable binding of the sulfonamide-functionalized indolones.

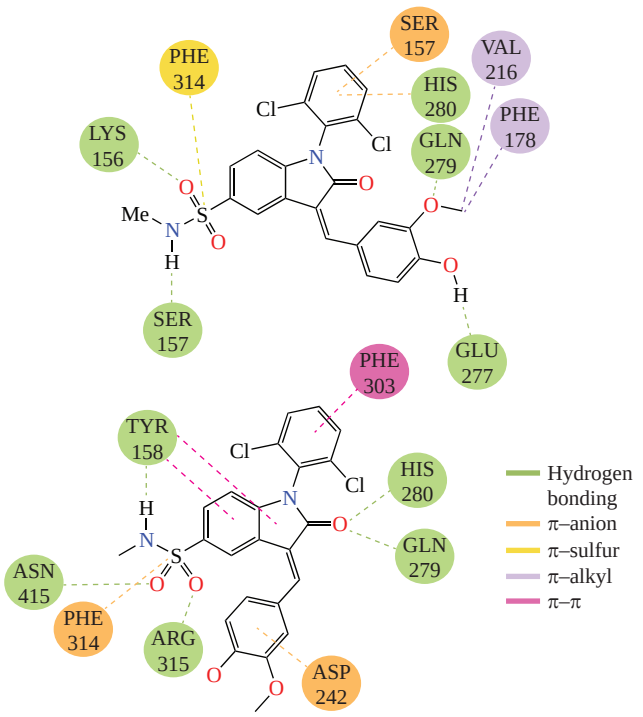


Figure 2 2D model for comparison of the interaction between the protein and *Z*/*E*-**5e**.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.06.033.

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