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Research Article

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Synthesis, characterization and structure activity relationship analysis of N-acetyl-2-substituted phenyl thiazolidine-4-carboxylic acids derivatives as neuraminidase inhibitors

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ABSTRACT

Thiazolidines were easily obtained in yields of 63-95% from the condensation of L-Cysteine and alkoxybenzaldehyde under slightly conditions. This condensation afforded product as a mixture of diastereomers, Cis-(2R,4R) and Trans-(2S,2R), which could not be separated. An equilibrium resulting from epimerization at C(2) occurs between two isomers. The Cis/Trans ratios were strongly dependent on the nature of the solvent. QSAR techniques increase the probability of success and reduce time and coast in drug discovery process. The study presented QSAR investigation on 6 bioactive arylthiazolidines that have activity Urease inhibition. Molecular descriptors, logP, HOMO, polarization, molecular weight and Hydration energy were calculated. Initial geometry optimizations were carried out with the AM1 Hamiltonian. Several models for the predication of biological activity have been drawn up by using the multiple regression technique. Seven models with r^2 ranges from 0.68-0.98 were predicted. A model with penta - parametric linear equation with r^2 value of 0.98 was used to predict the biological activities, the agreement between the observed and the predicted values was up to 98%. All the target compounds (25 compounds) were tested for their ability to Neuraminidase inhibition. Preliminary result showed that some of the compounds displayed enhanced inhibitory activities (IC_{50}=64.10 – 11.76 µM) compared to the Oseltamivir .

Keywords: Urease inhibition, Thiazolidines, QSAR

INTRODUCTION

Currently, heterocyclic compounds have been extensively studied due to their important properties and applications. Among these compounds, thiazol and thiazolidine derivatives have become especially noteworthy in recent years [1,2]. Thiazolidine derivatives has an interesting biological activities, some of these are anticancer activity [3,4], antioxidant [5] and also has an interesting antimicrobial activity [6,7].

Inflenza, a viral infection of the upper respiratory tract in humans, has plagued mankind since the dawn of history[8].Annually, influenza infection results in more than 500,000 deaths worldwide[9]. There are two main types of influenza virus: type A and type B. These two types are responsible for seasonal flu epidemics each year [9].Therefore, antivirals also play an important role in the prevention and management of influenza. There two classes of antiviral agents for influenza: adamantanes and neuraminidase inhibitors. Neuraminidase inhibitors(NAIs)are effective against all human, avian and animal influenza viruses [10]. NAIs inhibit the release of virions by competitively inhibiting viral NA, which is a key glycoprotein at the surface of the virus. Currently there are two NAIs drugs which have been approved worldwide: Oseltamivir and Zanamiver. Both drugs are approved for treatment of actue uncomplicated illness due to influenza A and B, and are also approved for preventive use [11]. Computer plays an escalating role in the design of new therapeutic agents in the field of bioorganic and medicinal chemistry [12]. To the best of our knowledge, the NA inhibition activity of this class of compounds has not been reported so far which makes this as a first report. This prompted us to investigate their structure-activity relations. A

detailed quantitative structure activity relationship (QSAR) analysis has been carried out on the thiazolidines reported herein by correlating their structural features and physicochemical properties with the activity to identify the important structural components in deciding the NA inhibition. This present report describes synthesis, characterized and QSAR studies of the thiazolidines derivatives.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR spectra were recorded on Brucker-500MHz spectrometer in DMSO-d6 and $CDCl_3$ solvents in the presence of TMS as an internal standard. Chemical shifts are reported with reference to the respective residual solvent or deuterated peaks (δ_H2.5) & (δ_H7.25) respectively. Coupling constants are reported in hertz. The abbreviation used are as follows: s (singlet), d (doublet), t (triplet), and dd (doublet of doublets).

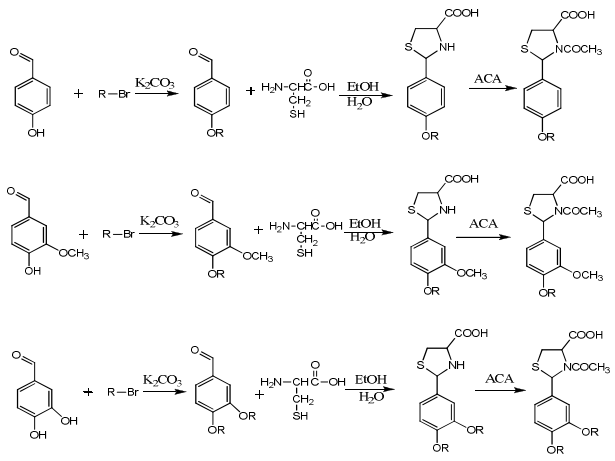
2.1.1 General Procedure for the Preparation of 2- Aryl-Thiazolidine-4-Carboxylic Acids [13].
A mixture of L-cysteine (3.16 g,0.026 mole) and appropriate aldehyde (0.026 mole) in ethanol (300ml) and water (30ml) was stirred at room temperature for 6-15h, and the precipitated solid was collected by filtration, washed with diethyl ether, and dried to afford 2-aryl-thiazolidine-4-carboxylic acid in 70-99% yield. General structure is shown in Fig. 1

2.1.2 General procedure for the Synthesis of N-Acetyl-2-Substituted phenyl thiazolidine -4-carboxylic Acids
All compounds were synthesized using the same procedure [14]. A representative example is described for N-Acetyl-2-phenyl thiazolidine-4-carboxylic acid.

A solution of Z1 (2.09 g, 0.01 mole) in 6% aqueous $NaCO_3$ (25 ml) cooled in ice- bath, followed by dropwise addition of acetic anhydride (2.04 g,0.02 mole) over 2 min.. The mixture was left stirred for 1h, and the with the aid of saturation with NaCl product was isolated by acidification of the reaction mixture and extraction with ethyl acetate (2x50 ml). The combined extracts was washed with saturated NaCl, dried over anhydrous Na_2SO_4 . Evaporation of solvent afford a solid recrystallized from ethyl acetate to give N-Acetyl-2-phenyl thiazolidine-4-carboxylic acid as white crystals (mp. 149-150° C, 78 % yield).

Structures, physical data, and symbols of synthesized compounds are shown in table (3).

Scheme 1



ACA = Acetic Anhydride , R = Methyl, Butyl, Decanyl, Cetyl and benzyl

(2R, 4R)-2-phenylthiazolidine-4-carboxylic acid(Z1) (Cis isomer) (61%).
Yield: 92 mp: 159-160C° ^{1}HNMR(500MHz, $CDCl_3$) δ 5.29(s, 1H), 2.33(m, 1H), 3.7 (dd, 1H, J=8.63, 7.32Hz), 2.9(dd, 1H, J=10.28, 8.74Hz), 3.24(dd, 1H, J=10.33, 7.25Hz), 7.27 (d, 1H, J=1.52Hz), 7.13(t, 1H, J=1.64Hz), 7.00(t, 1H, J=7.33Hz), 7.07(t, 1H, J=1.49Hz), 7.22(d, 1H, J=7.37Hz).

(2S, 4R)-2-phenylthiazolidine-4-carboxylic acid (Z1) (Trans isomer) (39%).
Yield: 92% mp: 159-160C° ^{1}HNMR (500MHz, $CDCl_3$) δ 5.56 (s, 1H), 2.33(m, 1H), 3.96(t, 1H, J=5.91Hz), 2.99(dd, 1H, J=10.2851, 5.58Hz), 3.14(dd, 1H, J=10.51, 7.15Hz), 7.27(d, 1H, J=1.52Hz), 7.13(t, 1H, J=1.64Hz), 7.00(t, 1H, J=7.33Hz), 7.07(t, 1H, J=1.49Hz), 7.22(d, 1H, J=7.37Hz).

(2R, 4R)-2-(4-hydroxyphenylthiazolidine-4-carboxylic acid (Z2) (Cis isomer) (29%).
Yield: 93 mp: 167-169C° ^{1}H NMR (500 MHz, DMSO d6) δ 5.54 (s, 1H), 8.69(br, s, 1H), 4.23(dd, 1H, J=6.97, 4.04), 3.14(dd, 1H, J=10.23, 4.04Hz), 3.26(br, 1H, J=7.32Hz), 7.28(d, 1H, J=8.31Hz), 6.69(d, 1H, J=8.31Hz).

(2S, 4R)-2-(4-hydroxyphenyl)thiazolidine-4-carboxylic acid (Z2) (Trans isomer) (71%).
Yield: 93 mp: 167-169C° ^{1}HNMR (500 MHz, DMSO d6) δ 5.39(s, 1H), 8.69(br, s, 1H), 3.81 (br, 1H, J=7.84), 3.04(dd, 1H, J=10.9, 5.68Hz), 3.34(dd, 1H, J=10.9, 7.37Hz), 7.30 (d, 1H, J=8.33Hz), 6.73(d, 1H, J=8.33Hz).

(2R, 4R)-2-(4-methoxyphenyl)thiazolidine-4-carboxylic acid (Z3) (Cis isomer) (35%).
Yield: 83 mp: 164-166C° ^{1}HNMR (500 MHz, DMSO d6) δ 5.41 (s, 1H), 8.70 (br, s, 1H), 3.83 (t, 1H, J=7.8), 3.04(t, 1H, J=9.24Hz), 3.34(dd, 1H, J=10.03Hz),7.35(d, 1H, J=8.14Hz), 6.85 (d, 1H, J=8.25Hz).

(2S,4R)-2-(4-methoxyphenylthiazolidine-4-carboxylic acid (Z3) (Trans isomer)(65%).
Yield: 83 mp: 164-166C° ^{1}H NMR(500MHz, DMSO d6) δ 5.88(s, 1H), 8.73(br, s, 1H), 4.19 (dd, 1H, J=8.30, 5.74), 3.03(dd, 1H, J=10.1, 6.5Hz), 3.22(dd, 1H, J=10.1, 6.5), 7.56 (d, 1H, J=7.86Hz), 7.16(t, 1H, J=7.5Hz), 7.35(t, 1H, J=7.5Hz).

(2R, 4R)-2-(4-butoxyphenyl)thiazolidine-4-carboxylic acid (Z4) (Cis Isomer) (72.72%).
Yield: 79% mp: 147-149C° ^{1}HNMR(500MHz, $CDCl_3$) δ 5.60(s, 1H), 2.57 (m, 1H, J=1.8Hz), 3.95(dd, 1H, J=24.33, 5.38Hz), 3.30(dd, 1H, J=34, 10.25Hz), 3.50(t, 1H, J=6.56Hz), 7.81(d, 1H, J=8.73Hz), 6.98 (d, 1H, J=8.72Hz), 6.82(d, 1H, J=8.67Hz), 7.45(d, 1H, J=8.49Hz), 4.15(t, 2H, J=6.35Hz), 1.76(m, 2H, J=7.62Hz), 1.46(m, 2H, J=7.26Hz), 0.95(t, 3H, J=4.8Hz).

(2S, 4R)-2-(4-butoxyphenyl)thiazolidine-4-carboxylic acid(Z4)(TransIsomer) (27.27%).
Yield: 79% mp: 147-149C° ^{1}HNMR (500 MHz, $CDCl_3$) δ 5.74 (s, 1H), 2.57 (m, 1H, J=1.8Hz), 4.030(t, 1H, J=6.47Hz), 3.30(dd, 1H, J=34, 10.25Hz), 3.67(d, 1H, J=6.98Hz), 7.81(d, 1H, J=8.73Hz), 6.98(d, 1H, J=8.72Hz), 6.82(d, 1H, J=8.67, Hz), 7.45 (d, 1H, J=8.49Hz), 4.15(t, 2H, J=6.35Hz), 1.76 (m, 2H, J=7.62Hz), 1.46(m, 2H, J=7.26Hz), 0.95(t, 3H, J=4.8Hz).

(2R, 4R)-2-(4-(hexadecyloxy)phenyl)thiaz-olidine-4-carboxylic acid (Z6) (Cis Isomer) (71%).
Yield: 65% mp: 139-140C° ^{1}HNMR (500MHz, $CDCl_3$) δ 5.49 (s, 1H), 2.50 (t, 1H, J=1.79Hz), 3.86 (dd, 1H, J=25,6. 14Hz), 3.15(dd, 1H, J=21, 7.91Hz), 3.42 (dd, 1H, J=21.18, 7.27Hz), 7.36 (d, 1H, J=8.63Hz), 6.76(d, 1H, J=8.75Hz), 6.78(d, 1H, J=8.67Hz), 7.36(d, 1H, J=8.63Hz), 4.27(t, 2H), 1.69(m, 2H, J=4.51Hz), 1.35(m, 2H, J=7.09Hz), 1.18(m, 24H, J=5.15Hz), 0.80(t, 3H, J=7.09Hz).

(2S, 4R)-2-(4-(hexadecyloxy)phenyl)thiazol- idine-4-carboxylic acid (Z6) (Trans Isomer) (29%).
Yield: 65% mp: 139-140C° ^{1}HNMR (500MHz, $CDCl_3$) δ 5.69 (s, 1H), 2.50(t, 1H, J=1.79Hz), 3.96 (dd, 1H, J=28.3, 6.48Hz), 3.24(t, 1H, J=5.61Hz), 3.42(dd, 1H, J=21.18, 7.27Hz), 7.36 (d, 1H, J=8.63Hz), 6.76(d, 1H, J=8.75Hz), 6.78(d, 1H, J=8.67Hz), 7.36(d, 1H, J=8.63Hz), 4.15 (t, 2H, J=6.35Hz), 1.76(m, 2H, J=7.62Hz), 1.46(m, 2H, J=7.26Hz), 0.95(t, 3H, J=4.8Hz).

(2R, 4R)-2-(4-(benzyloxy)phenyl)thiazolidi- ne-4-carboxylic acid (Z7) (Trans Isomer) (66.67).
Yield: 71% mp: 166-167C° ^{1}HNMR(500MHz, $CDCl_3$) δ 5.45(s, 1H), 2.43(s, 1H), 3.97(s, 1H), 3.12(s, 1H), 3.35(s, 1H), 7.35(d, 2H, J=7.2Hz), 6.81(s, 2H), 4.93(s, 2H), 7.17-7.29(m, 5H).

(2S, 4R)-2-(4-(benzyloxy)phenyl)thiazolid- ine-4-carboxylic acid (Z7) (Trans Isomer) (33.33).
Yield: 71% mp: 166-167C° ^{1}HNMR(500MHz, $CDCl_3$) δ 5.4563(s, 1H), 2.43(s, 1H), 4.29 (s, 1H), 3.24(s, 1H), 3.42(t, 1H),7.68 (d, 2H, J=5.52Hz), 6.94 (d, 2H, J=5.82Hz), 5.01 (s, 2H), 7.17-7.29(m, 5H).

(2R, 4R)-2-(4-hydroxy-3-methoxy phenyl thiazolidine-4-carboxylic acid (Z8) (Cis isomer)(32%).
Yield: 95 mp: 163-165C° ^{1}HNMR(500MHz, DMSO d6) δ 5.52(s, 1H), 8.90(br, 1H), 4.28 (dd, 1H, J=6.82, 3.57Hz), 3.27(t, 1H, J=7.35Hz), 3.16(dd, 1H, J=10.1, 3.45Hz), 7.01(s, 1H), 6.73(d, 1H, J=7.88Hz), 6.83(d, 1H, J=7.88Hz), 3.75(s, 3H).

(2S, 4R)-2-(4-hydroxy-3-methoxy phenyl thiazolidine-4-carboxylic acid (Z8) (Trans isomer) (68%).
Yield: 95 mp: 163-165C° ^{1}H NMR(500 MHz, DMSO d6) δ 5.37(s, 1H), 8.89(br, 1H), 3.83 (t, 1H, J=8.61Hz), 3.05(t, 1H, J=9.33Hz), 3.32(t, 1H, J=9.72Hz), 7.07(s, 1H), 6.68(d, 1H, J=8.1Hz), 6.88(d, 1H, J=7.88Hz), 3.75(s, 3H).

(2R, 4R)-2-(4-butoxy-3-methoxyphenyl) thiazolidine-4-carboxylic acid (Z10) (Cis isomer) (64.58%)
Yield: 84% mp: 146-148C° ^{1}HNMR(500MHz, $CDCl_3$) δ 5.47(s, 1H), 2.54(s, 1H), 3.92 (m, 1H, J=5.04Hz), 3.12(t, 1H, J=9.39Hz), 3.43(t, 1H, J=7.83Hz), 7.02(s, 1H), 6.78(d, 1H, J=11.23Hz), 6.99(d, 1H, J=10.98Hz), 4.19(t, 2H, J=5.78Hz), 1.75(d, 2H, J=7.06Hz), 1.43(d, 2H, J=7.06Hz), 0.92(t, 3H, J=6.96Hz, 3.82(s,3H).

(2S, 4R)-2-(4-butoxy-3-methoxyphenyl) thiazolidine-4-carboxylic acid(Z10)(Trans isomer)(35.42. %)
Yield: 84% mp: 146-148C° ^{1}HNMR (500MHz, $CDCl_3$) δ 5.69(s, 1H), 2.54 (s, 1H), 3.64 (d, 1H, J=7.03Hz), 3.23(dd, 1H, J=20.77, 5.41Hz), 3.37 (t, 1H, J=7.81Hz), 7.02(s, 1H), 6.78(d, 1H, J= 11.23Hz), 6.99(d, 1H, J=10.98Hz), 4.19(t, 2H, J=5.78Hz), 1.75(d, 2H, J=7.06Hz), 1.43 (d, 2H, J=7.06Hz), 0.92(t, 3H, J=6.96Hz, 3.82(s, 3H).

(2R, 4R)-2-(4-(decyloxy)-3-methoxyphenyl) thiazolidine-4-carboxylic acid (Z11) (Cis Isomer)(66.59%).
Yield: 73% mp: 133-136C° ^{1}HNMR (500MHz, $CDCl_3$) δ 5.41(s, 1H), 2.49(s, 1H), 3.87 (dd, 1H, J=28.4, 6.88Hz), 3.07(t, 1H, J=10.15Hz), 3.42(dd, 1H, J=20.6, 7.31Hz), 6.97(s, 1H), 6.73(d, 1H, J=8.78Hz), 6.96(d, 1H, J=8.15Hz), 4.15(t, 2H, J=6.35Hz), 1.76(m, 2H, J=7.62 Hz), 1.46(m, 2H, J=7.26Hz), 0.78(t, 3H, J=7.03Hz), 4.13(t, 3H, J=6.88Hz).

(2S, 4R)-2-(4-(decyloxy)-3-methoxyphenyl) thiazolidine-4-carboxylic acid (Z11) (Trans Isomer)(33.41)
Yield: 73% mp: 133-136C° ^{1}HNMR (500MHz, $CDCl_3$) δ 5.66(s, 1H), 2.49(s, 1H), 3.84 (dd, 1H, J=28.4, 6.88Hz), 3.17(dd, 1H, J=21.12, 10.1Hz), 3.42(dd, 1H, J=21.03, 7.31Hz), 6.97 (s, 1H), 6.7 (d, 1H, J=8.00Hz), 6.96(d, 1H, J=8.15Hz), 4.15(t, 2H, J=6.35Hz), 1.72 (m, 2H, J=5.75Hz), 1.33(d, 2H, J=7.58Hz), 1.16(s, 12H), 0.78(t, 3H, J=7.03Hz), 4.13 (t, 3H, J=6.88Hz).

(2R, 4R)-2-(4-(benzyloxy)-3-methoxyphen- yl)thiazolidine-4-carboxylic acid(Z13) (Cis Isomer)(68.62%).
Yield: 70% mp: 138-140C° ^{1}HNMR (500MHz, $CDCl_3$) δ 5.46(s, 1H), 2.54 (s, 1H), 3.90 (dd, 1H, J=16.7, 7.47Hz), 3.12 (dd, 1H, J = 20.5, 8.74Hz), 3.36 (dd, 1H, J=20.7, 7.29Hz), 7.35(d, 2H, J=7.2Hz), 6.81(s, 2H), 5.09 (d, 2H, J=7.07Hz), 6.93. 7.04(m, 3H, J=1.81Hz), 7.30-7.33(m, 2H), 6.776.81(m, 2H, J=8.33Hz), 7.37(d, 1H, J=7.32Hz), 3.86(s, 1H).

(2S, 2R)-2-(4-(benzyloxy)-3-methoxyphen-yl)thiazolidine-4-carboxylic acid (Z13) (Trans Isomer) (31.37%).
(Yield: 70% mp: 138-140C° ^{1}HNMR (500MHz, $CDCl_3$) δ 5.69 (s, 1H), 2.54(s, 1H), 3.18(t, 1H, J=7.08Hz), 3.22(dd, 1H, J=20.5, 8.74Hz), 3.36(dd, 1H, J=20.7, 7.29Hz), 7.35(d, 2H, J=7.2Hz), 6.81(s, 2H), 5.09(d, 2H, J=7.07Hz), 6.93.7.04(m, 3H, J=1.81Hz), 7.37.33(m, 2H), 6.776.81(m, 2H, J=8.33Hz), 7.37(d, 1H, J=7.32Hz), 3.86(s, 1H).

(2R, 4R)-2-(3,4-dibutoxyphenyl)thiazolidi- ne-4-carboxylic acid (Z15) (Cis Isomer) (62.34%).
Yield: 80% mp: 148-150C° ^{1}H NMR (500MHz, $CDCl_3$) δ 5.39 (s, 1H), 2.48(t, 1H, J=1.8Hz), 3.88(dd, 1H, J=16.3, 6.96Hz), 3.05(dd, 1H, J=20.5, 8.81Hz), 3.37(dd, 1H), J=20.7, 7.27Hz), 6.95(s, 1H), 6.76.74(d, 1H, J=8.23Hz), 6.9-6.92 (d, 1H, J=8.49Hz), 3.82-3.91 (t, 4H, J=7.34Hz), 1.69(m, 2H, J=3.19Hz), 1.40(m, 4H, J=3.58Hz), 0.86(m, 6H, J=3.1Hz).

(2S, 4R)-2-(3,4-dibutoxyphenyl) thiazolidine carboxylic acid (Z15) (Trans Isomer) (37.65%).
Yield: 80% mp: 148-150C° ^{1}HNMR (500MHz, $CDCl_3$) δ 5.63 (s, 1H), 2.48(t, 1H, J=1.8Hz), 4.13(dd, 1H, J=14.4, 5.55Hz), 3.16(dd, 1H, J=21.26, 5.44Hz), 3.30(dd, 1H), J=21.23, 7.3Hz), 7.81(d, 1H, J=8.73Hz), 6.7-6.74(d, 1H, J=8.23Hz), 6.96.92(d, 1H, J=8.49 Hz), 3.823.91 (t, 4H, J=7.34Hz), 1.69(m, 2H, J=3.19Hz), 1.40(m, 4H, J=3.58Hz), 0.86(m, 6H, J=3.1Hz).

(2R, 4R)-2-(3,4-bis(decyloxy)phenyl) thiazolidine-4-carboxylic acid (Z16) (Cis Isomer) (56.52%).
Yield: 73% mp: 128-130C° ^{1}H NMR (500MHz, $CDCl_3$) δ 5.45 (s, 1H)**,** 2.48 (t, 1H, J=1.8Hz)**,** 4.43(s, 1H)**,** 3.3(dd, 1H)**,** 3.48(s, 1H)**,** 7.4(s, 1H)**,** 6.84(s, 1H)**,** 7.05(d, 1H, J=8.49Hz)**,** 3.98(s, 4H)**,** 1.8(s, 2H)**,** 1.45(s, 4H)**,** 1.27(s, 12H)**,** 0.88(t, 6H, J=6.6Hz**).**

(2S, 4R)-2-(3,4-bis(decyloxy)phenyl) thiazolidine-4-carboxylic acid (Z16) (Trans Isomer) (43.47).
Yield: 73% mp: 128-130C° ^{1}H NMR (500MHz, $CDCl_3$) δ 5.53 (s, 1H)**,** 2.48 (t, 1H, J=1.8Hz)**,** 4.43(s, 1H)**,** 3.3(dd, 1H)**,** 3.48(s, 1H)**,** 7.4(s, 1H)**,** 6.84(s, 1H)**,** 7.05(d, 1H, J=8.49Hz)**,** 3.98(s, 4H)**,** 1.8(s, 2H)**,** 1.45(s, 4H)**,** 1.27(s, 12H)**,** 0.88(t, 6H, J=6.6Hz**).**

(2R, 4R)-2-(3,4-bis(hexadecyloxy)phenyl) thiazolidine-4-carboxylic acid (Z17) (Cis Isomer) (50%)
Yield: 68% mp: 96-100C° ^{1}HNMR (500MHz, $CDCl_3$) δ 5.35(s, 1H), 2.48 (t, 1H, J=1.8Hz), 4.20(s, 1H), 3.01(t, 1H, J=9.05Hz), 3.48(d, 1H, J=9.75Hz), 7.4(s, 1H), 6.84(s, 1H), 7.05(d, 1H, J=8.49Hz), 3.83(t, 4H, J=9.75Hz), 1.67(s, 2H), 1.38(s, 2H), 1.22(s, 24H), 0.84(s, 3H, J=6.6Hz).

(2S, 4R)-2-(3,4-bis(hexadecyloxy)phenyl) thiazolidine-4-carboxylic acid (Z17) (Trans Isomer) (50%).
Yield: 68% mp: 96-100C° ^{1}HNMR (500MHz, $CDCl_3$) δ 5.50(s, 1H), 2.48(t, 1H, J=1.8Hz), 4.43(s, 1H), 3.24(t, 1H, J=5.75Hz), 3.33(t, 1H, J=7.4Hz), 6.78(d, 1H, J=6.65), 6.83(d, 1H), 3.83(t, 4H, J=9.75Hz), 1.67(s, 2H), 1.38(s, 2H), 1.22(s, 24H), 0.84(s, 3H, J=6.6Hz).

(2R, 4R)-3-acetyl-2-phenylthiazolidine-4-carboxylicacid(AZ1)(CisIsomer)(93.33%)
Yield: 80% mp: 149-150C° ^{1}HNMR (500MHz, $CDCl_3$) δ 6.05(s, 1H), 5.06(t, 1H, J=6.8Hz), 3.32(dd, 1H, J=24.17, 6.66Hz), 3.36(dd, 1H, J=24.14, 6.98Hz), 11.13 (s, 1H), 1.98(s, 3H), 7.57(d, 1H, J=7.51Hz), 7.35, 7.38(t, 2H, J=7.68Hz), 3.27-7.30 (t, 1H, J=7.4Hz).

(2S, 4R)-3-acetyl-2-phenylthiazolidine-4-carboxylic acid(AZ1) (Trans Isomer) (6.67%).
Yield: 80% mp: 149-150C° ^{1}HNM(500MHz, $CDCl_3$) δ 6.39 (s, 1H), 4.8(s, 1H), 3.42 (d, 1H, J=6.4Hz), 3.42(d, 1H, J=6.4Hz), 11.13(s, 1H), 2.19(s, 3H), 7.57(d, 1H, J=7.51Hz), 7.35-7.38 (t, 2H, J=7.68Hz), 3.27-7.30(t, 1H, J=7.4 Hz).

(2R, 4R)-3-acetyl-2-(4-methoxyphenyl)thiaz olidine-4-carboxylic acid (AZ2) (Cis Isomer)(13.34 %).
Yield: 72% mp:177-179C° ^{1}HNMR(500MHz, $CDCl_3$) δ 5.96 (s, 1H), 4.89 (t, 1H, J=6.89 Hz), 3.22(d, 2H, J=6.89Hz), 1.85(s, 3H), 7.54(d, 2H, J=8.56Hz), 6.82(d, 2H, J=8.59, 3.73(s, 3H).

(2S, 4R)-3-acetyl-2-(4-methoxyphenyl) thiazolidine-4-carboxylic acid (AZ2) (Trans Isomer)(13.34 %).
Yield: 72% mp: 177-179C° ^{1}HNMR (500M Hz, $CDCl_3$) δ 6.26 (s, 1H), 4.7 (s, 1H), 3.35(t, 2H, J=8.61Hz), 2.08(s, 3H), 7.44(d, 2H, J=8.15Hz), 6.73(d, 2H, J=8.01Hz), 3.73(s, 3H).

(2R, 4R)-3-acetyl-2-(4-(hexadecyloxy) phenyl)thiazolidine-4-carboxylic acid (AZ6) (Cis Isomer) (77.94 %).
Yield: 72% mp: 177-179C° ^{1}HNMR(500MHz, $CDCl_3$) δ 5.05(s, 1H), 5.09(t, 1H, J=6.39Hz), 3.32 (dd, 1H, J=24.24, 6.67Hz), 3.46(dd, 1H, J=24.2, 6.22Hz), 9.91(s, 1H), 2.02(s, 3H), 7.43 (d, 2H, J=8.62Hz), 6.91(d, 2H, J=8.59Hz), 3.97(t, 2H, J=6.51Hz), 1.81(m, 2H, J=7.6Hz), 1.45(t, 2H, J=7.2Hz), 1.29(s, 24H), 0.91(t, 3H, J=6.7Hz).

(2S, 4R)-3-acetyl-2-(4-(hexadecyloxy) phenyl)thiazolidine-4-carboxylic acid (AZ6) (Trans Isomer) (22.94 %).
Yield: 72% mp: 177-179C° ^{1}HNMR(500MHz, $CDCl_3$) δ 5.05(s, 1H), 5.09 (t, 1H, J=6.39Hz), 3.32(dd, 1H, J=24.24, 6.67Hz), 3.46 (dd, 1H, J=24.2, 6.22Hz), 9.91(s, 1H), 2.21(s, 3H), 7.86(d, 2H, J=8.73Hz), 7.02(d, 2H, J=8.7Hz), 4.07 (t, 2H, J=6.55Hz), 1.81(m, 2H), J=7.6, 1.45(t, 2H, J=7.2Hz), 1.29(s, 24H), 0.91(t, 3H, J=6.7Hz).

(2R, 4R)-3-acetyl-2-(4-(benzyloxy) phenyl)thiazolidine-4-carboxylic acid (AZ7) (Cis Isomer) (83.05%).
Yield: 70% mp: 98-101C° ^{1}HNMR (500M Hz, $CDCl_3$) δ 6.20(s, 1H), 4.48(t, 1H, J=6.4Hz), 3.16(dd, 1H, J=20.3, 7.44Hz), 3.16(dd, 1H, J=20.3, 7.44Hz), 9.77(s, 1H), 1.80(s, 3H), 6.84(d, 2H, J=8.62Hz), 7.39(d, 2H, J=8.30Hz), 4.91(s, 2H), 7.49 (d, 2H, J=8.6Hz), 7.19-7.33 (m, 3H).

(2S, 4R)-3-acetyl-2-(4-(benzyloxy) phenyl) thiazolidine-4-carboxylic acid (AZ7) (Trans Isomer)(16.94%).
Yield: 70% mp: 98-101C° ^{1}HNMR(500MHz, $CDCl_3$) δ 5.92(s, 1H), 4.69 (d, 1H, J=4.82Hz), 3.30 (dd, 1H, J=22.2, 6.64Hz), 3.30 (dd, 1H, J=22.2, 6.64Hz), 9.77 (s, 1H), 2.04(s, 3H), 6.97(d, 2H, J=8.69Hz), 6.81(s, 2H), 5.05(s, 2H), 7.72 (d, 2H, J=6.94Hz), 7.19-7.33 (m, 3H).

(2R, 4R)-3-acetyl-2(3,4-dimethoxyphenyl)thiazolidine-4-carboxylic acid (AZ8) (Cis Isomer) (89.47%).
Yield: 63% mp: 176-178C° ^{1}HNMR(500MHz, $CDCl_3$) δ 5.97(s, 1H), 4.92(t, 1H, J=6.90Hz), 3.25 (d, 1H, J=6.92Hz), 3.25(d, 1H), J=6.92, 10 (s, 1H), 2.08(s, 3H), 7.45(d, 1H, J=1.79Hz, 6.77 (d, 2H, J=8.26Hz), 7.03(d, 1H, J=1.8Hz), 3.83(s, 3H), 3.81(s, 3H).

(2S, 4R)-3-acetyl-2-(3,4-dimethoxyphen- yl)thiazolidine-4-carboxylic acid (AZ8) (Trans Isomer)(10.53%).
Yield: 63% mp: 176178C° ^{1}HNMR(500 MHz, CDCl3) δ 6.29 (s, 1H), 4.76(s, 1H), 3.36(dd, 1H, J=24.57, 5.0Hz), 3.36(dd, 1H, J=24.57, 5.0Hz), 10.0(s, 1H), 2.08(s, 3H), 7.23(s, 1H), 6.72(d, 2H, J=8.23Hz), 7.04(d, 1H, J=1.84Hz), 3.83(s, 3H), 3.81(s, 3H).

(2R, 4R)-3-acetyl-2-(4-butoxy-3-methoxyphenyl)thiazolidine-4-carboxylic acid (AZ10) (Cis Isomer) (78.53%).
Yield: 76% mp: Oil ^{1}HNMR(500MHz, $CDCl_3$) δ 6.00(s, 1H)**,** 5.04(m, 1H, J=6.17Hz)**,** 3.29-3.43(m, 1H, J=6.28Hz)**,** 3.29-3.43(m, 1H, J=6.28Hz**,** 10 (s, 1H)**,** 1.97(s, 3H)**,** 7.32(s, 1H)**,** 6.85(d, 2H, J=7.98Hz)**,** 6.98(d, 1H, J=7.91Hz)**,** 3.83(s, 3H)**,** 2.032.3(m, 2H)**,** 1.47(m, 2H,7.29Hz)**,** 0.96(t, 3H, J=7.19Hz)**,** 3.85(s, 3H)**.**

(2S, 4R)-3-acetyl-2-(4-butoxy-3-methoxyphenyl)thiazolidine-4-carboxylic acid(AZ10) (Trans Isomer) (21.46%).
Yield: 76% mp: Oil ^{1}HNMR(500MHz, $CDCl_3$) δ 6.03(s, 1H)**,** 4.85(m, 1H, J=6.17Hz)**,** 3.99(t, 1H, J=6.68Hz)**,** 3.99(t, 1H, J=6.86Hz)**,** 10(s, 1H)**,** 2.00(s, 3H)**,** 7.43(s, 1H)**,** 6.81(d, 2H, J=8.16Hz)**,** 6.99(d, 1H, J=7.26Hz)**,** 3.83(s, 3H)**,** 2.03-2.3(m, 2H)**,** 1.80 (t, 2H, 7.24Hz)**,** 1.23 (t, 3H, J=7.18Hz)**,** 3.85(s, 3H)**.**

(2R, 4R)-3-acetyl-2-(4-(hexadecyloxy)-3-methoxyphenyl)thiazolidine-4-carboxylic acid(AZ12) (Cis Isomer) (91.42%).
Yield: 68% mp: 45-50C^o ^{1}HNMR(500MHz, CDCl3) δ 6.03(s, 1H)**,** 5.08(t, 1H, J=6.6Hz)**,** 3.42(m, 1H, J=15.5, 6.6Hz)**,** 3.35(dd, 1H, J=24.2, 6.71Hz)**,** 10(s, 1H)**,** 2.00(s, 3H)**,** 7.22(s, 1H)**,** 6.86(d, 2H, J=8.16Hz), 6.99 (d, 1H, J=5.3 Hz)**,** 4.02 (t, 2H, J= 6.86Hz), 1.831.92(m, 2H, J=3.0Hz), 1.47(m, 2H, J=7.12Hz)**,** 1.33 (m, 24H, J=7.38Hz)**,** 0.91 (t, 3H, J=6.7Hz)**,** 3.88(s, 3H)

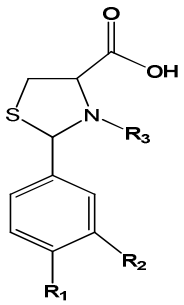
(2S, 4R)-3-acetyl-2-(4-(hexadecyloxy)-3-methoxyphenyl)thiazolidine-4-carboxylic acid(AZ12) (Trans Isomer) (8.58%).
Yield: 68 mp: 45-50C^o ^{1}HNMR(500MHz, $CDCl_3$) δ 6.03(s, 1H)**,** 5.18(s, 1H)**,** 2.95 (t, 1H, J=8.88Hz)**,** 3.45(dd, 1H, J=15.5, 6.6Hz)**,** 10(s, 1H)**,** 2.00(s, 3H)**,** 7.44(d, 1H, J=1.76Hz)**,** 7.45(d, 2H, J=1.84Hz)**,** 7.47(d, 1H, J=1.85Hz)**,** 4.13(t, 2H, J=6.86Hz)**,** 1.83-1.92(m, 2H, J=3.0Hz)**,** 1.47(m, 2H, J=7.12Hz)**,** 1.33(m, 24H, J=7.38Hz)**,** 0.91(t, 3H, J=6.7Hz), 3.95(s,3H)**.**

(2R, 4R)-3-acetyl-2-(3,4-dibutoxy phenyl)thiazolidine-4-carboxylic acid(AZ15) (Cis Isomer) (94.11 %).
Yield: 81% mp: 149-152C^o ^{1}HNMR(500MHz, CDCl3) δ 5.99(s, 1H)**,** 5.05(t, 1H, J=6.7Hz)**,** 3.30(dd, 1H, J=24.15, 6.7Hz)**,** 3.37(dd, 1H, J=24.15, 6.75Hz)**,** 11.01(s, 1H)**,** 1.98(s, 3H)**,** 7.26(s, 1H)**,** 6.82(d, 2H, J=8.3Hz)**,** 7.22(d, 1H, J=1.9Hz)**,** 3.98(t, 4H, J=6.65Hz), 1.78(m, 4H, J=6.5Hz)**,** 1.48(m, 4H, J=7.3Hz)**,** 0.95(m, 6H, J=7.35Hz)**.**

(2S, 4R)-3-acetyl-2-(3, 4-dibutoxy phenyl)thiazolidine-4-carboxylic acid AZ15) (Trans Isomer) (5.89 %).
Yield: 81% mp: 149-152C^o ^{1}HNMR(500MHz, $CDCl_3$) δ 6.3(s, 1H)**,** 4.85(s, 1H)**,** 11.01 (s, 1H)**,** 2.18(s, 3H), 7.26(s, 1H)**,** 7.0 (d, 2H, J=1.85Hz)**,** 7.02(d, 1H, J=1.95Hz)**,** 3.98(t, 4H, J=6.65Hz)**,** 1.78(m, 4H, J=6.5Hz)**,** 1.48(m, 4H, J=7.3Hz)**,** 0.95(m, 6H, J=7.35Hz).

Computational details

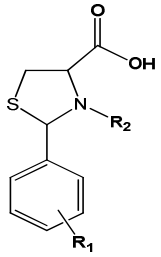
The studied Arylthiazolidine have been taken with their reactivity from literature [15]. Chemical structures and experimental biological activities are gathered in Table 1. Biological activities are presented as IC_{50}. Molecular descriptors for the studied compounds, logP, Refractivity (Ref), Polaraizability (Pol),Hydration energy, Molecular weight, Molecular Volume, HOMO and LUMO energies were calculated using Hyper Chem 8.5 program, after geometry optimization with the semi empirical RM1 Hamiltonian. The general molecular structure of the studied molecules is shown in Fig.1.



R_1, R_2 = Methoxy, butoxy, decyloxy-, cetyloxy- and benzyloxy- .
R_3=H or CH_3CO-

Fig.1.General structure of thiazolidine derivatives

Table 1.The structures and in vitro Urease inhibition activity IC_{50}



Com. No	R_1	R_2	IC_{50} (µM)
1	-H	H	21.3
2	o-OH	H	20.2
3	o-COOH	H	18.1
4	p-CN	H	23.4
5	o-NO_2	H	22.5
6	o-OH,m-OCH_3	H	12.3

RESULTS AND DISCUSSION

The reaction of L-cysteine with benzaldehyde or its derivatives in the presence of ethanol and water as solvent (6:4) in either yields phenyl thiazolidine-4-carboxylic acid and its derivatives, which in turn will react with acetic anhydride to form N-acetyl phenyl thiazolidine-4-carboxylic acid and its derivatives as shown in scheme 1.

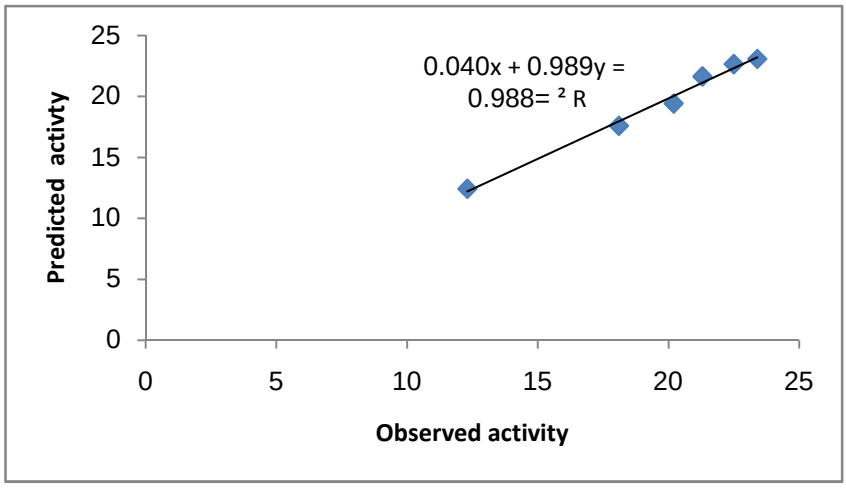


Fig. 2 Observed and predicted values of IC_{50} for thiazolidine by using Eq.7

Table 2 : The values of the descriptors and the predicted activity(IC_{50}) by Eq.7

Comp. No.	Log P	HOMO	Polari. A^3	MW (g/mole)	IC_{50obs}	IC_{50pred}	Residual
1	0.98	-8.733527	22.07	209.26	21.3	21.64	-0.34
2	-0.04	-8.999312	22.71	225.26	20.2	19.42	0.78
3	0.37	-8.865118	24.63	253.27	18.1	17.59	0.51
4	0.71	-9.011923	23.93	234.27	23.4	23.07	0.33
5	0.17	-9.555171	23.91	254.26	22.5	22.65	-0.15
6	-1.04	-8.69868	25.18	255.29	12.3	12.43	-0.13

All the synthesized thiazolidines and its analogs were screened for Neuraminidase inhibitors studies. Six models were predicated in this study and have been build up with the use of the following descriptors: log P, energy of HOMO (ε HOMO) (ev), Polarization (A^3), Molecular weight (MW) (g/mole) and Hydration energy (HE) (Kcal./mole).

The first model is a two parameter equation (Eq.1) with one descriptors, the best one-variable model contains log P as the correlating parameter. This model is shown below.

IC_{50}= 4.7458 logP + 18.723 (1)
n=6 r^2= 0.68 s =2.52 F=8.81

Here and hereafter, n is the number of compounds used, r^2 is the coefficient of variance ,s is the standard error of estimation and F is the Fisher's statistics or F-ratio between variances of calculated and observed value.

Table 3: Calculated Urease inhibitory activity of the target compound

Sym	R_1	R_2	R_3	IC_{50} (µM)	Sym.	R_1	R_2	R_3	IC_{50} (µM)
Z1	H	H	H	21.78	AZ1	H	H	$COCH_3$	22.34
Z2	OH	H	H	18.16	AZ2	OCH_3	H	$COCH_3$	18.20
Z3	OCH_3	H	H	20.00	AZ6	Hexadecyloxy	H	$COCH_3$	30.00
Z4	Butoxy	H	H	28.72	AZ7	Benzyloxy	H	$COCH_3$	11.76
Z6	Hexadecyloxy	H	H	64.10	AZ8	OCH_3	OCH_3	$COCH_3$	20.21
Z7	Benzyloxy	H	H	26.53	AZ10	Butoxy	OCH_3	$COCH_3$	55.75
Z8	OH	OCH_3	H	15.08	AZ12	Hexadecyloxy	OCH_3	$COCH_3$	32.15
Z10	Butoxy	OCH_3	H	22.85	AZ15	Butoxy	Butyoxy	$COCH_3$	38.29
Z11	Decyloxy	OCH_3	H	39.95	AZ18	Benzyloxy	Benzyloxy	$COCH_3$	21.48
Z13	Benzyloxy	OCH_3	H	26.31					
Z15	Butoxy	Butyoxy	H	30.79	Oseltamivir			0.2	
Z16	Decyloxy	Decanoxy	H	66.84					

This eq. 1 shows that even a single parameter, log P, explains 68% of variation in the activity (IC_{50}), that is, a increase in the magnitude of log P is favorable for exhibition of IC_{50}. In the other words, a increase in the number of carbon chain increase IC_{50}.

The second model is the three- parametric model (Eq.2) with two descriptors gave better statistical parameters log P and ε HOMO, the successive regression analysis indicated that by adding of ε HOMO to the one equation, there is an appreciable improvement in the statistics which is demonstrated by the following model.

IC_{50} = 4.4171 log p – 6.2407 HOMO – 37.2382 (2)
n=6 r^2= 0.91 s =1.51 F= 16.36

In this model the positive coefficient of the added parameter, namely HOMO makes a favorable contribution to the exhibition of IC_{50}. positive values of log P and negative values of ε HOMO, suggest that the biological activity increase with an increase in ε log P and HOMO.

The third model is the four- parametric model (Eq.3) with three descriptors log P ,ε HOMO and polarization ,further step –wise regression indicated the occurrence of a best three- variable model containing polarization as the additional correlating parameters. Only a slight improvement in statistics was observed accordingly for the following regression expression in equation 3.

IC_{50} = 3.3114 log P – 4.957 HOMO – 1.07 Polz. (3)
n=6 r^2= 0.91 s =1.54 F= 15.59

Another four –parametric model Eq.4 with the same descriptor gave the better statistical parameters.

IC_{50} = 3.75 log P – 6.4 HOMO – 0.628 Polz.-23.658 (4)
n=6 r^2=0.93 s=1.62 F=9.68

The Fourth model with five parameters, the four-variable model is found to contain Hydration Energy in addition to other three parameters(logP, HOMO and Polarization). The improvement in the statistics is considerably high.

IC_{50} = 3.817 log P – 4.755 HOMO – 1.21 Polz.– z.-0.379 HE. (5)
n=6 r^2=0.94 s=1.55 F=10.54

Another model with the same number of descriptor.

IC_{50} = 4.09 log P – 6.00 HOMO – 0.816 Polz. – 0.332 HE – 19.997 (6)
n=6 r^2=0.95 s=1.86 F=5.6

But the best four –variable model is found contain Molecular weight in addition to other three – variable (log P, HOMO and Polarization).There is an appreciable improvement in the statistics which is demonstrated by the following model.

IC_{50} = 3.05 log P -11.545 HOMO+ 2.85 Polz. – 0.25 MW – 92.757 (7)
n=6 r^2=0.98 s=0.97 F=21.05

Where:
IC_{50} is the molar concentration of the drug leading to 50% inhibition of influenza neuraminidase(NA).
HOMO is Highest unoccupied molecular orbital.
HE is Hydration Energy.
Log P is Partition Coefficient.
MW is Molecular weight.

In the above equation n is the number of thiazolidine compounds have taken with their reactivity from literature [15], which used to drive the QSAR model.

The best model concerning the present study the five-parametric equation 7.

All the target compounds were tested for their ability to inhibit NA. Preliminary result showed that some of the compounds (21 compounds) displayed enhanced inhibitory activities (IC_{50}= 64.10 - 11.76 µM) compared to the lead compound Z1 are shown in table3. The amino-acetyl-thiazolidines showed the high activities compared to amino-thiazolidines and the order of increasing activity in R2,R3 and R4 are H,OH and OH, H,Ph-CH_2- and Ph-CH_2- , H,CH_3O- and CH_3O-, CH_3CO-, CH_3O- and CH_3O-, and CH_3CO-, CH_3O- and $CH_3CH_2CH_2CH_2O$- . The most potent compound is AZ7 (IC_{50} =11.76 µM) , which is the mixture of AZ7 $_{anti}$ (the major product) and AZ7 $_{syn}$ (the minor product).

The predicated activity of the studied thiazolidine derivatives as calculated by Eq.7 are shown in table 2 , in addition a comparison between observed and predicated values of IC_{50} for thiazolidine derivatives used in the development of Eq.6 is shown in Fig.2.

CONCLUSION

Thiazolidines were easily obtained in yields of 63-95% from the condensation of L-Cysteine and alkoxybenzaldehyde under slightly conditions. This condensation afforded product as a mixture of diastereomers, Cis-(2R,4R) and Trans-(2S,2R), which could not be separated. An equilibrium resulting from epimerization at C(2) occurs between two isomers. The Cis/Trans ratios were strongly dependent on the nature of the solvent. In CDCl3 the major isomer was the Cis Isomer while in DMSO-d_6, the trans diastereoisomer predominated after complete equilibration. The study indicated that QSAR of biological activity represented by IC_{50} of arylthiazolidine amides against human prostate cancer cells can be modeled with the semi empirical RM1 based quantum mechanical molecular descriptors. The hepta - parametric regression equation is the best produced model with very good statistical fit as evident from its R^2=0.98, F=21.05 and s=0.97. It is evident from the results that the inhibition of the prostate cancer influenced mainly by molecular weight and surface area.

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