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Sonochemical synthesis of 2-substituted nicotinic acid ethyl ester derivatives: Their *in vitro* and *in silico* evaluation against SIRT1

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ABSTRACT

Based on the initial docking studies of a representative compound *in silico* the evaluation of SIRT1 inhibitory potential of 2-substituted nicotinic acid ethyl ester derivatives was undertaken *in vitro*. A sonochemical method was developed and employed for the faster synthesis of this class of compounds. The methodology involved the iodine-mediated reaction of β-enamino esters with allylic alcohols in aqueous DMSO in the presence of air under mild conditions. A number of 2-substituted nicotinic acid ethyl ester derivatives were synthesized by employing this ultrasound assisted method in good to acceptable yield. The use of less expensive iodine and aqueous media, milder reaction condition and shorter reaction time are the key advantages of the current approach. All the synthesized compounds were tested for their SIRT1 inhibitory potential *in vitro* when some of them showed good activities and the compound **3g** being the best among them. The docking studies suggested that the fused lactone ring of **3g** played a key role in interacting with the SIRT1 *in silico via* formation of H-bonds. The overall outcome of the *in vitro* and *in silico* studies suggested the compound **3g** as an initial hit molecule for further pharmacological studies.

1. Introduction

The nicotinic acid or pyridine-3-carboxylic acid (**A**, Fig. 1) and its derivatives constitute an important class of *N*-heterocyclic compounds that have found numerous applications and importance in both chemistry and biology. For example, as the most common form of water soluble vitamin B3, also known as niacin [1], the nicotinic acid has the potential to influence DNA repair, genomic stability, and the immune system, eventually having an impact on cancer risk [2]. Indeed, its importance for genomic stability thereby possibility of reducing the cancer risk has been studied and documented [3]. Besides, the use of nicotinic acid in clinical practice for the treatment of dyslipidemia is well known [4]. Nevertheless, nicotinic acid and its derivatives have gained considerable interest in the discovery and development of promising anticancer agents. Accordingly, the synthesis as well as evaluation of a range of novel derivatives of nicotinic acid has been reported for this purpose [5a–c]. In another study [6] nicotinic acid has been reported to attenuate the vascular inflammation *via* modulation of SIRT1 pathway [6a]. Notably, SIRT1 [or Sirtuin1, a NAD(+)-dependent class III histone deacetylase (HDACs) is one of the 7 members (SIRT1-SIRT7) in the sirtuin family in mammals] is known to participate in the regulation of cellular inflammation [6b]. On the other hand, being considered as important targets for cancer therapeutics [7a–d] sirtuins are shown to up-regulated in various types of cancer whereas inhibition of sirtuins allows re-expression of silenced tumor suppressor genes, leading to the decreased growth of cancer cells. Further, the nicotinamide **B** (Fig. 1) a derivative of nicotinic acid has been reported to be one of the earliest inhibitors of sirtuins including SIRT1 [7c]. All these reports and observations as well as our interest in this area [8a,b] prompted us to explore the template **C** derived from **A** for the identification of new and potential inhibitors of SIRT1. The substituent R^1 was introduced at the C-2 position of the pyridine ring (i) due to the key role played by the C-2 substituents in the anticancer activities [9a,b] and (ii) to con-

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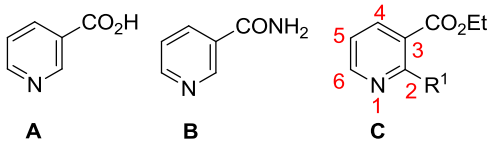


Fig. 1. Nicotinic acid **A**, nicotinamide **B** and the template **C**.

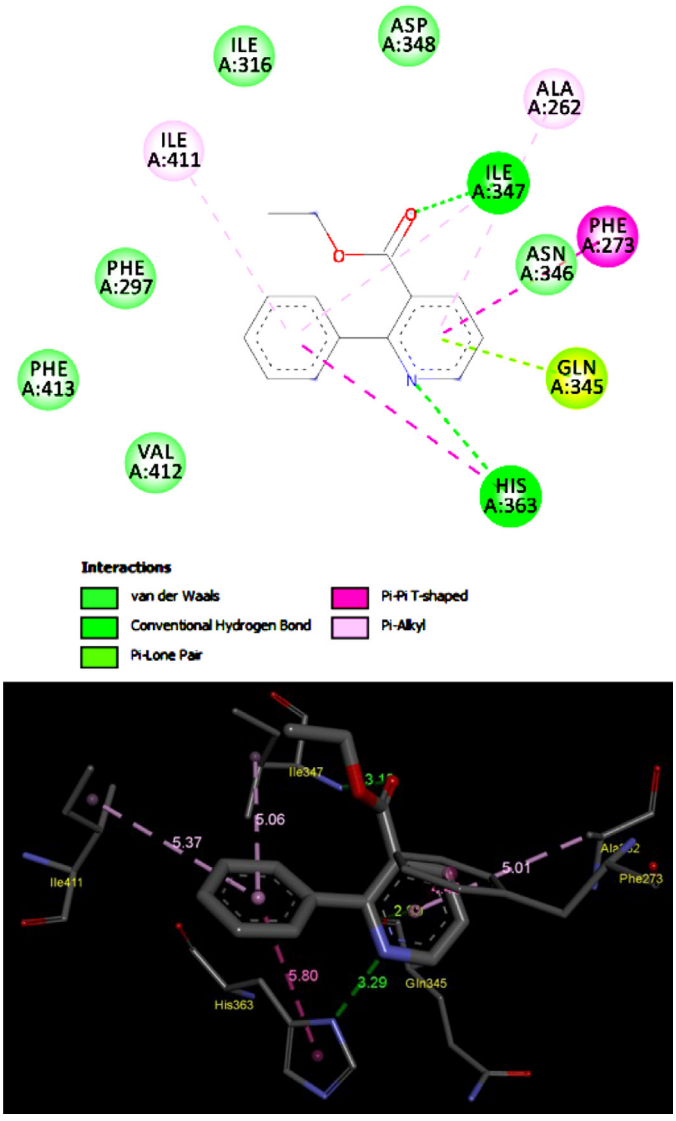


Fig. 2. Binding interactions and docked pose of compound **C-1** at the catalytic site of SIRT1 (PDB: 4I5I).

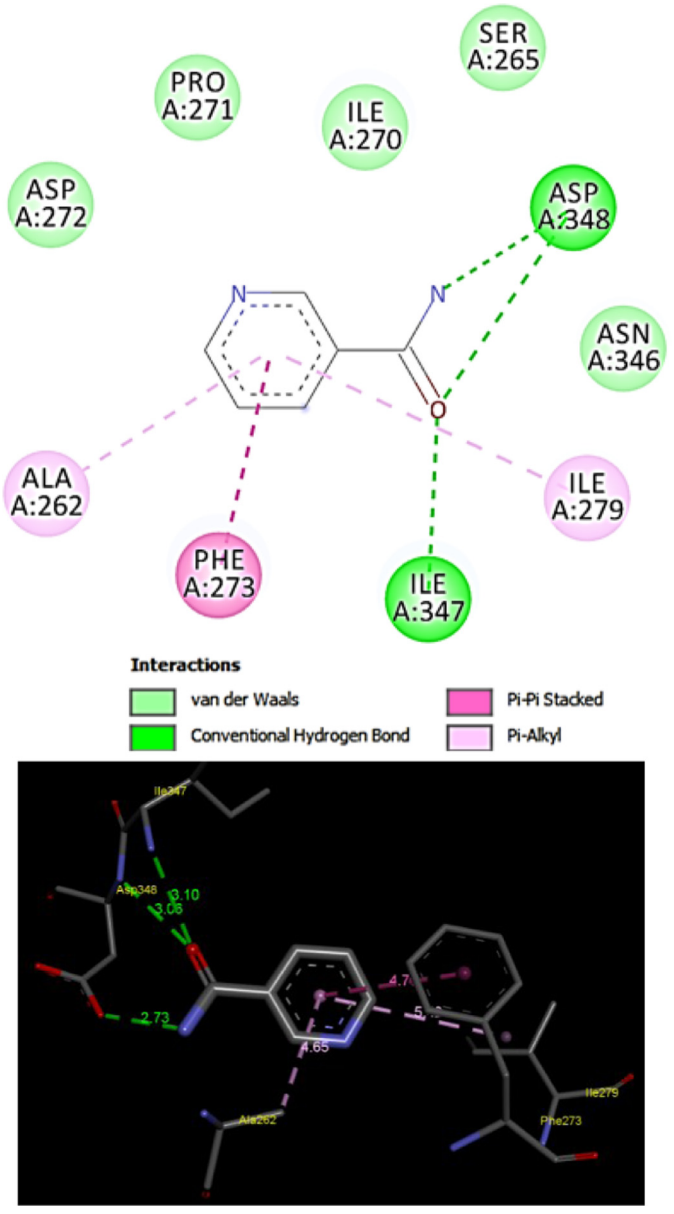


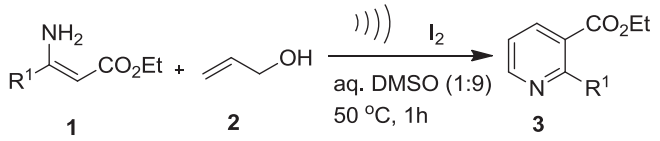
Fig. 3. Binding interactions and docked pose of nicotinamide at the catalytic site of SIRT1 (PDB: 4I5I).

struct a library of small molecules based on **C** via varying the substituent R^1 for studying the Structure-Activity-Relationship (SAR) within the series thereby identifying the best active molecules. Notably, our current research effort is of particular interest because the discovery of novel agents is considered as one of the way forwards to address the multifaceted problem of drug resistance [10]. The drug resistance is known to be a major cause in the failure of chemotherapy based approaches on several occasions.

To assess the merit of template **C** the *in silico* docking studies of a representative molecule **C-1** were carried out using the SIRT1 protein (PDB: 4I5I) (Fig. 2, see also Fig S-1 in suppl data). The compound **C-1** showed good binding with the catalytic residues of SIRT1 with the binding energy of -90.39 kcal/mol that was comparable to nicotinamide's -88.38 kcal/mol. The molecule participated in the H-bond interactions with HIS363 and ILE347 through its pyridine nitrogen atom and the ester carbonyl group, respectively. Notably, a similar H-bond interaction with ILE347 was shown by nicotinamide through its amide carbonyl moiety (Fig. 3, see also Fig S-2 in suppl data). Further, **C-1** also interacted with other residues such as ALA262, ILE347, GLN345, HIS363, ILE411, PHE297 and PHE273 commonly through the van der Waals, pi-pi, pi-lone pair and pi-alkyl interactions in the catalytic domain of SIRT1. The outcome of this *in silico* studies encouraged us to gain a direct and convenient access to the compound **C-1** and its analogues for further evaluation.

2. Results and discussion

The 2-aryl substituted pyridine derivatives are commonly prepared [11] by Pd-catalyzed direct arylation of pyridine *N*-oxides [11a] or by addition of Grignard reagents to pyridine *N*-oxides followed by treatment with Ac_2O [11b]. They are also prepared *via* $AlCl_3$ induced C-C bond forming reactions between 2-halopyridines



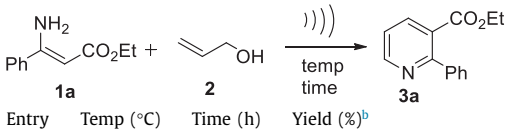
Scheme 1. Sonochemical synthesis of 2-substituted nicotinic acid ethyl ester derivatives.

and arenes [12]. More recently, this class of compounds has been prepared *via* the reaction of aryl ketone with 1,3-diaminopropane in the presence of a catalyst or reagents such as $Cu(OSO_2CF_3)_2$ [13], LiCl [14], I_2-HCl [15], $Ru(2,2'\text{-bipyridine})_3Cl_2.6H_2O$ [16] and $Pd(OAc)_2$-PTSA-O_2 [17]. In our effort the synthesis of 2-substituted nicotinic acid ethyl ester derivatives were carried out earlier *via* the IBX (2-iodoxybenzoic acid) mediated reaction of β-enamino esters with allylic alcohols [18]. While this one-pot reaction proceeded under a metal free conditions however the methodology involved the use of an elevated temperature (70 °C) and relatively longer reaction time (3h). Moreover, the oxidant IBX though readily available but is not an inexpensive reagent. On the other hand, ultrasound plays an important role in accelerating the reaction rate substantially affording the desired product within short reaction time. Further, the ultrasound assisted reactions (i) are considered as green approaches in organic synthesis [19], (ii) are effective in waste minimization and reduction of energy requirements [20] and (iii) play key role in developing new, cost effective and environmentally safe methodologies for accessing numerous organic molecules [21,22]. We therefore decided to adopt ultrasound assisted method for the faster access of our target compounds based on **C**. Notably, during this study we found that the elemental iodine in aqueous DMSO was an effective as well as cheaper alternative agent for the reaction of β-enamino esters (**1**) with allylic alcohols (**2**) under ultrasound irradiation (Scheme 1). Notably, molecular iodine or iodine containing agents have found considerable applications in organic synthesis [23–25] and we have a long term interest in this area [26–28].

Firstly, a brief study was carried out to establish the optimized reaction conditions and the reaction of (*E*)-ethyl 3-amino-3-phenylacrylate (**1a**) with allyl alcohol (**2**) in aqueous DMSO (1: 9 H_2O-DMSO) was used as a model reaction for this purpose. The reaction was performed at 30 °C for 3 h in the presence of air under ultrasound using a laboratory ultrasonic bath SONOREX SUPER RK 510H model producing irradiation of 35 kHz. No catalyst or reagent was used in this case and the reaction did not proceed at this or elevated temperature (entry 1 and 2, Table 1). Notably, the reaction was completed within 1h affording the desired product **3a** in good yield when IBX was used (entry 3, Table 1). Next we explored the use of elemental iodine as an inexpensive and alternative agent for the current transformation. Indeed, we were encouraged by the fact that the use of iodine for the oxidation of allylic alcohol (protected or unprotected) has been reported previously [29]. To our satisfaction the reaction proceeded well in the presence of iodine affording the product **3a** in 74% yield (entry 4, Table 1). The reaction was carried out using 1.5 equivalent of iodine when the use of lower quantity of iodine decreased the product yield significantly (entry 5, Table 1). The product yield was decreased further when the reaction was performed in the absence of ultrasound even at higher temperature for a longer time (entry 6, Table 1). Overall, the reaction condition of entry 4 appeared to be optimum for the preparation of **3a** and was used for the preparation of its analogues.

A number of 2-substituted nicotinic acid ethyl ester derivatives (**3**) were synthesized by employing various β-enamino esters (**1**). The ultrasound assisted reaction in the presence of iodine under open air proceeded well in all these cases affording the desired

Table 1
Effect of conditions on the reaction of **1a** with **2**.[a]



Entry	Temp (°C)	Time (h)	Yield (%)[b]
1	30	3	0
2	50	3	0
3	50	1	71[c]
4	50	1	74[d]
5	50	1	43[e]
6	80	5	29[f]

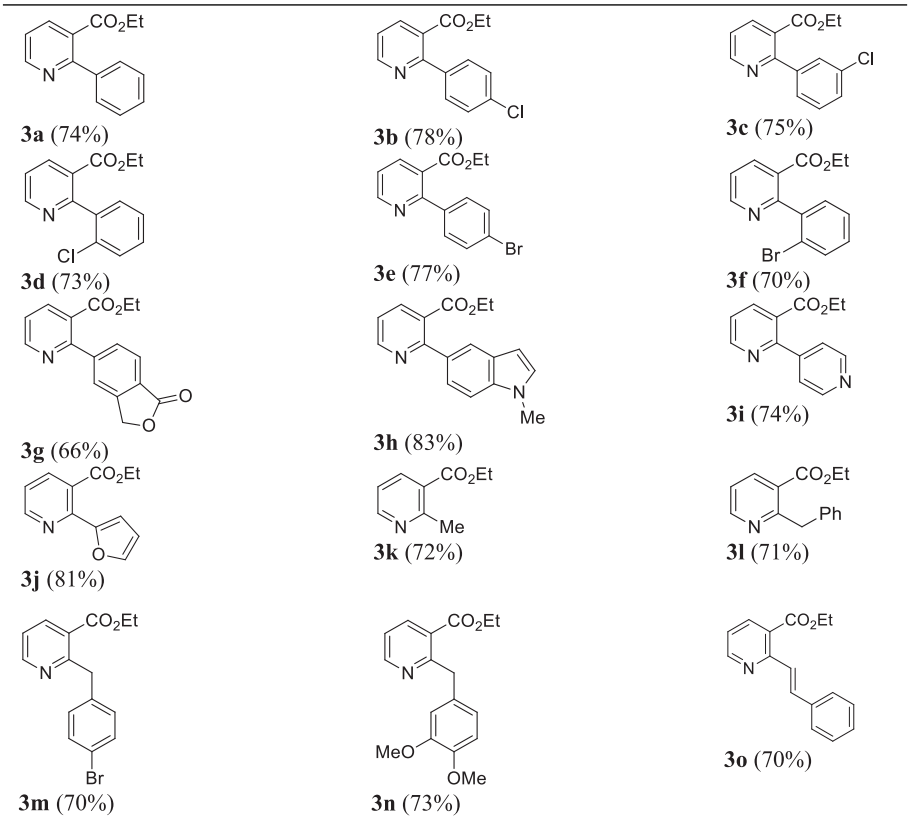
[a] All reactions were performed using the β-enamino ester **1a** (0.4 mmol) and allyl alcohol **2** (0.8 mmol.) in aqueous DMSO (1:9, 5 mL) under open air.
[b] Isolated yields.
[c] The reaction was performed in the presence of IBX (1.2 equiv.).
[d] The reaction was performed in the presence of elemental iodine (1.5 equiv.).
[e] 0.8 equiv. iodine was used.
[f] The reaction was performed in the absence of ultrasound.

products in good to acceptable yields (Table 2). The C-2 substituent of the product **3** may include a substituted aryl ring, a phthalide or indole or pyridine or furan ring, a methyl or substituted benzyl moiety or a styryl group. The key advantages of the current approach are the use of less expensive iodine and aqueous media, milder reaction condition and shorter reaction time. Moreover, since the reaction was performed under open air hence the methodology is free from the risk of pressure development as observed in case of reaction performed in an isolated system especially in the large scale preparation.

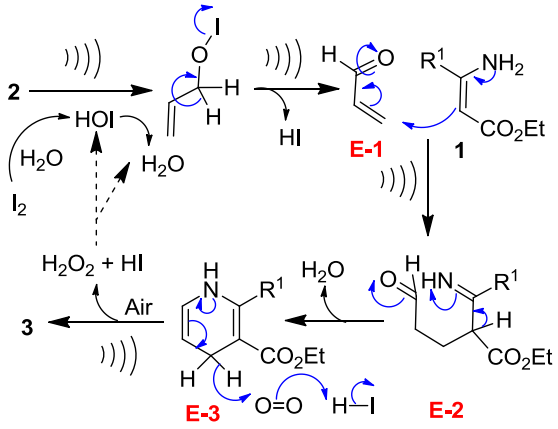
All the compounds synthesized were characterized by spectral (^{1}H and ^{13}C NMR and HRMS) data. This is exemplified by the partial ^{1}H and ^{13}C NMR spectral data of two representative compounds e.g. **3g** and **3h** (see Fig S-0 in suppl data). A triplet near 1.1 δ and a quartet near 4.2 δ in the ^{1}H NMR spectra was due to the OEt (ester) protons of **3g** whereas a singlet near 5.3 δ accounting two protons was due to its methylene moiety of the fused lactone ring. Similarly, the OEt protons appeared near 1.0 and 4.1 δ in case of **3h** whereas a triplet near 6.5 δ, a doublet near 7.1 δ and a singlet near 3.8 δ were due to the C-3, C-2 and NMe protons of the indole ring, respectively. The C-6 proton of the pyridine ring appeared near 8.8 or 8.7 δ in both the cases. The two C=O groups of fused lactone and the ester moiety and the OCH_2 carbon appeared near 170.7, 166.9 and 69.6 ppm, respectively in the ^{13}CNMR spectra of **3g** whereas the C-6 of the pyridine ring and the ester carbons appeared near 157.6, 61.7 and 13.7 ppm. In case of **3h** the key ^{13}C signals and the corresponding carbons were identified as 169.0 (C=O), 159.6 (C-6 of the pyridine ring), 101.7 (C-3 of the indole ring) and 32.9 (NMe) ppm. The IR absorption near 1760 and 1725 cm^{-1} in case of **3g** also indicated the presence of lactone and ester C=O group, respectively whereas rest of the compounds showed IR signal near 1720 cm^{-1} due to the ester moiety.

Based on the earlier reports [18,29] a plausible reaction mechanism for the I_2-mediated reaction of **1** with **2** under ultrasound irradiation is proposed in Scheme 2. The reaction seems to proceed *via* (i) ultrasound assisted disproportionation reaction of I_2 with water to generate hydroiodous acid (HOI) (along with HI) *in situ* [30], (ii) oxidation of allylic alcohol (**2**) by HOI (via providing the electrophilic I^+ species) [31] promoted by ultrasound to give the aldehyde **E-1** that on (iii) sonochemical Michael addition with β-enamino ester (**1**) followed by (iv) intramolecular cyclization gives the 1,4-dihydropyridine intermediate **E-3** *via* **E-2**, (v) oxidation of **E-3** in the presence of air under ultrasound to give the product **3**. Notably, HI along with water are the by-products formed during

Table 2.
List of 2-substituted nicotinic acid ethyl ester derivatives (**3**) synthesized following the method shown in Scheme 1.[a,b]



[a] All reactions were performed using the β-enamino ester **1** (0.4 mmol), allyl alcohol **2** (0.8 mmol), iodine (1.5 equiv.) in aqueous DMSO (1:9, 5 mL) under ultrasound irradiation in the presence of open air.
[b] Figure in the bracket represents the isolated yield.



Scheme 2. Proposed reaction mechanism for the I_2-mediated reaction of **1** with **2** under ultrasound irradiation in the presence of air.

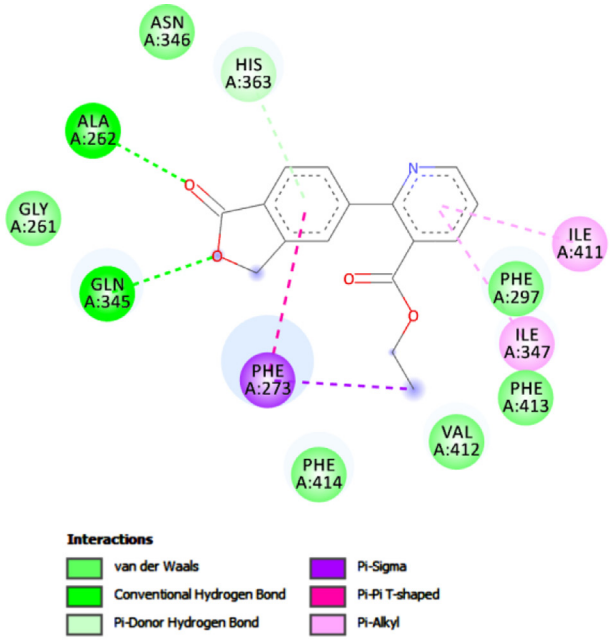
this transformation when HI participates in regenerating the HOI to complete the reaction cycle. It is evident from Table 1 that ultrasound not only accelerated the reaction rate but also facilitated the formation of the desired product. Indeed, the ultrasound facilitates cavitation involving the growth, oscillation, and collapse of bubbles under the action of an acoustic field [32,33]. Consequently, drastic conditions including the extremely high pressure (up to 1800 atmosphere) and temperature (e.g. 2000–5000 K) inside the medium within a very short duration are produced chiefly by the cavitational collapse. Additionally, the shear forces, jets, and shock waves are produced by this collapse outside the bubble. Thus, the overall effects induced by cavitation could be involved in the oxidation of **2** followed by Michael addition with **1** and subsequent intramolecular cyclization followed by oxidation (Scheme 2). Nevertheless, the combined effect of ultrasound, iodine and air was essential for the successful preparation of **3**.

All the 2-substituted nicotinic acid ethyl ester derivatives (**3**) synthesized were assessed for their inhibitory activities against SIRT1 *in vitro* using a reported biochemical enzymatic assay [34]. The known inhibitor nicotinamide (the reported IC_{50} value against SIRT1 = 120 μM) [35] was used as a reference compound. At the concertation of 10 μM the compounds that showed good activities (>50% inhibition) include **3a** (72% inhibition), **3g** (81% inhibition), **3h** (59% inhibition), **3i** (67% inhibition) and **3j** (53% inhibition) (see Table S-1 in suppl data). This was further supported by the estimated total energy of these molecules obtained *via* the *in silico* docking studies performed (using these compounds including nicotinamide) against the SIRT1 protein (PDB: 4I5I). The iGEMDOCK version2.1 software [36], a program for computing ligand conformation and orientation relative to the active site of the protein was used for the docking studies and results are presented in Table 3. The docking [37a-b] interactions occurred with the catalytic domain residues of 241-516. The binding interactions and docked pose of the best active molecule **3g** at the catalytic site of SIRT1 is shown in Fig 4 (see also Fig S-3 in suppl data). The molecule **3g** participated in the H-bond interactions with GLN345 and ALA262 through its lactone oxygen atom and the carbonyl group, respectively. Notably, similar involvement of its carbonyl group was also observed when the molecule was docked into other

Table 3
Summary of interactions of compounds with SIRT1 *in silico*.[a]

Compounds	Estimated Total Energy (kcal/mol)	Active site interacting residues
3a	-90.39	HIS363, ILE347, ALA262, ILE411, PHE273, GLN345
3g	-94.54	GLN345, ALA262, HIS363, PHE273, ILE347, ILE411
3h	-77.67	ALA262, ILE347, ILE411, PHE273, PHE297
3i	-88.46	HIS363, ILE347, ALA262, PHE273, GLN345
3j	-74.43	ALA262, HIS363, PHE273, ILE347, VAL412
Nicotinamide	-88.38	ASP348, ILE347, PHE273, ALA262, ILE279
EX527a	-110.5	ASP348, ILE347, ILE316, ILE279, PHE273, PHE297, ILE411, PHE413

[a] For binding interactions and docked pose see Fig S-3 to S-6 in the suppl data.



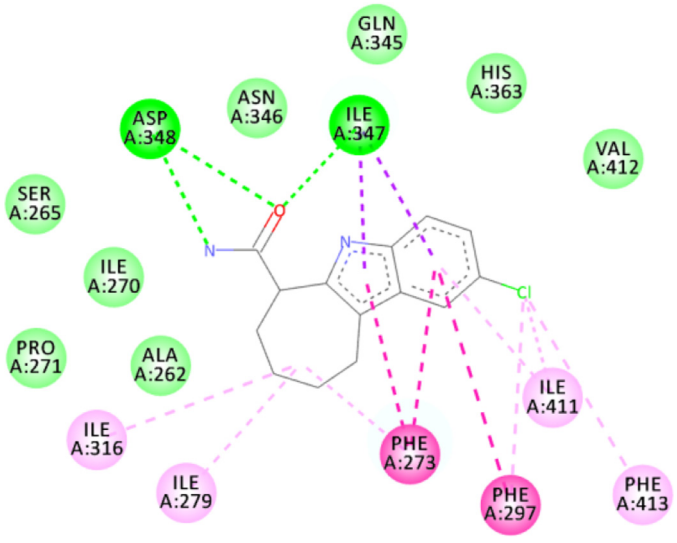


Fig. 5. 2D binding interactions and docked pose of EX527a at the catalytic site of SIRT1 (PDB: 4I5I).

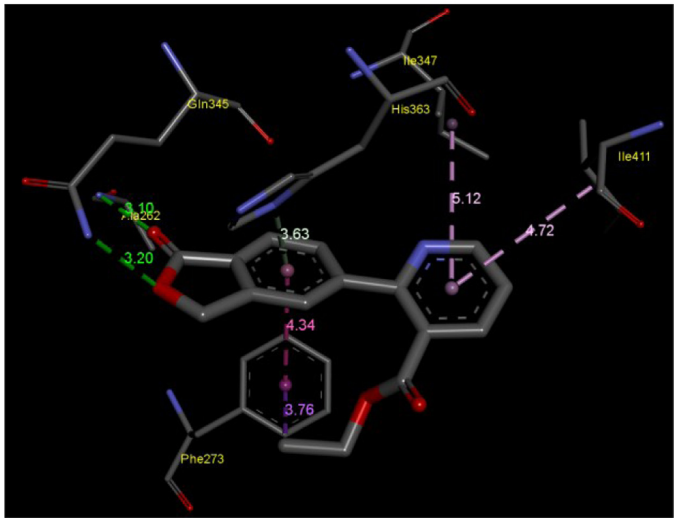


Fig. 4. Binding interactions and docked pose of compound **3g** at the catalytic site of SIRT1 (PDB: 4I5I).

SIRT1 with PDB code as 5BTR, 4ZZH and 4KXQ (see Fig S-7 in suppl data). Further, **3g** also interacted with other residues such as ILE347, HIS363, ILE411, PHE297, PHE273 etc *via* the van der Waals, pi-pi, pi-lone pair and pi-alkyl interactions in the catalytic domain of SIRT1. It is evident from Table 3 that **3g** showed better interactions with SIRT1 than nicotinamide as indicated by the outcome of *in vitro* assay. However, being a potent inhibitor of SIRT1 the indole derivative EX527a (an analogue of EX527 or Selisistat and also a co-crystallized ligand with PDB: 4I5I) [37a] showed superior energy and interactions (Table 3 and Fig. 5) than **3g**. Nevertheless, an acceptable ADME (absorption, distribution, metabolism, and excretion) or pharmacokinetic properties was predicted for **3g** when the computational ADME prediction of this compound along with **3a** and **3i** (that showed good inhibition of SIRT1) was carried out using Swiss ADME web-tool [38] (Table 4). Indeed, the molecule **3g** may show high GI absorption, favorable drug likeness as well as bioavailability score in addition to be a non-P-gp substrate though it may penetrate the blood brain barrier. Overall, the compound **3g** appeared as an interesting hit molecule for further biological studies.

From the viewpoint of Structure- Activity-Relationship (SAR) within the current series of 2-substituted nicotinic acid ethyl ester derivatives it was evident that the SIRT1 inhibitory activity was varied considerably with the change in the nature as well as type of substituent present at the C-2 position. In general, arene / heteroarene (e.g. indole, pyridine, furan etc.) moieties were favored at this position whereas an alkylaryl (e.g. benzyl or substituted benzyl) group at the same position was less effective. A smaller group e.g. Me or an alkenyl moiety like styrene at this position was also not favored. Notably, a halo benzene e.g. chloro or bromobenzene ring at the C-2 position decreased the activity whereas a descending order of activity was observed for the compound possessing phthalide > pyridine > indole > furan as the C-2 substituent.

Table 4.
Computational ADME prediction of selected compounds.

Properties	Molecules		
(i) Physicochemical	**3a**	**3g**	**3i**
Molecular Weight (g/mol)	227.26	283.28	228.25
Consensus Log P[a]	2.68	2.47	1.93
Log S (ESOL)[b]	-3.23 (soluble)	-3.12 (soluble)	-2.56 (soluble)
(ii) Pharmacokinetics			
GI[c] absorption	High	High	High
BBB[d] penetration	Yes	Yes	Yes
P-gp[e] substrate	No	No	No
(iii) Drug likeness			
Lipinski rule	Yes; 0 violations	Yes; 0 violations	Yes; 0 violations
Veber rule	Yes	Yes	Yes
Bioavailability score	0.55	0.55	0.55

[a] Log P: Lipophilicity.
[b] Log S (ESOL): water solubility, calculated by ESOL method which is a Quantitative Structure-Property Relationship (QSPR) based model.
[c] GI: Gastrointestinal.
[d] BBB: Blood Brain Barrier
[e] P-gp: permeability glycoprotein.

3. Conclusions

In conclusion, the 2-substituted nicotinic acid ethyl ester derivatives were assessed for their potential SIRT1 inhibitory properties *in vitro* that was backed by the initial docking studies of a representative compound *in silico*. Accordingly, a sonochemical method was developed and employed for the fast time for the quicker access to this class of compounds. The methodology involved the iodine-mediated reaction of β-enamino esters with allylic alcohols in aqueous DMSO in the presence of air under mild conditions. A number of 2-substituted nicotinic acid ethyl ester derivatives were synthesized by employing this ultrasound assisted method in good to acceptable yield. The use of less expensive iodine and aqueous media, milder reaction condition and shorter reaction time are the key advantages of the current approach. A plausible reaction mechanism is proposed and discussed for this sonochemical process. All the synthesized compounds were tested for their SIRT1 inhibitory potential *in vitro* when some of them showed good activities and the compound **3g** appeared to be the best among them. The docking studies suggested that the fused lactone ring of **3g** played a key role in interacting with the SIRT1 *in silico via* formation of H-bonds. An acceptable ADME or pharmacokinetic properties was predicted for **3g** via the computational ADME prediction of this compound *in silico*. Thus the overall outcome of the in vitro and in silico studies suggested the compound **3g** as an initial hit molecule for further pharmacological studies. Finally, the current research efforts not only revealed the utility of iodine and ultrasound for the rapid access of 2-substituted nicotinic acid ethyl ester derivatives but also highlighted the potential of nicotinic acid ethyl ester based framework for the identification of new inhibitors of SIRT1.

Credit author statement

Chandra Sekhar Challa and Devanna Nayakanti were involved in the preparation, isolation, purification and characterization of all the target compounds presented in the current manuscript.

Ravikumar Kapavarapu and Varadacharyulu Nallanchakravarthula was involved in performing all the *in silico* studies as well as in vitro assays.

Naresh Kumar Katari and Manojit Pal were responsible conceptualization, coordination and overall supervision of the entire work presented in the submitted manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.131069.

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