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Synthesis, Molecular Modeling and Biological Evaluation of Aza-flavanones as α-Glucosidase Inhibitors

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An efficient acid catalyzed methodology has been employed to synthesize a variety of aza-flavanones and their α-glucosidase inhibitory activity is evaluated using Acarbose, Miglitol and Voglibose as reference standards. Molecular modeling studies were performed for all compounds to identify important binding modes responsible for inhibition activity of α-glucosidase which helped to find key interactions between the enzyme and the active compounds. Among all the compounds **5g**, **5r** and **5w** have shown high α–glucosidase inhibition activity compared to standard reference drugs and identified as promising potential antidiabetic agents. It is the first biological evaluation of aza-flavanones as α-glucosidase inhibitors.

1. Introduction

Diabetes is one of the global chronic metabolic human diseases which results due to inadequate insulin secretion or inefficient utilization of insulin. Among the two major types of diabetes[1], type 2 diabetes is the critical which is characterized by hyperglycemia.[2] Hyperglycemia causes serious destruction to the body parts like kidneys, heart, eyes and other nervous systems. α-Glucosidase is an enzyme which catalyzes the conversion of carbohydrates to absorbable monosaccharides results increase in blood glucose levels. Inhibition of α-glucosidase can delay digestive process leads to the decrease in sugar levels in the blood. α-Glucosidase inhibition is identified as a therapeutic target to cure diabetes. The recent standard glucosidase inhibitors in clinical practice viz., Acarbose, Miglitol, Voglibose are associated with various side effects like bloating, flatulence, diarrhea, pain and their synthesis involved in multi steps. Hence, there is strong demand for discovery of improved α-glucosidase inhibitors for the treatment of diabetes.

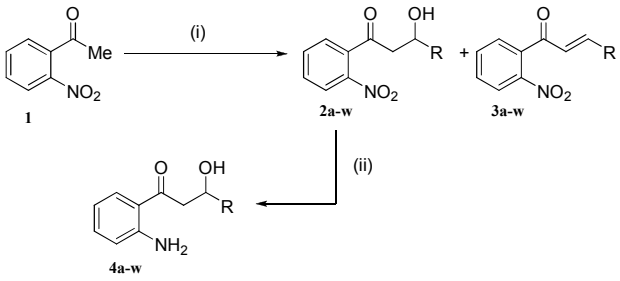
2-Aza-flavanones are an important class of building blocks in organic chemistry[3] and having potent biological and pharmaceutical properties like anti-cancer[4], antibacterial.[5] 2-Aza-flavanones regulate cell cycle by inhibiting microRNA which leads to the control of tumor progression.[6] Furthermore, these scaffolds also play a vital role in drug development.[7] Careful literature study revealed that synthesis and applications of aza-flavanones are limited.[8-11]

Most of the reports in the literature involved either cyclization of amino chalcones by aza-Michael addition[8-10] or by asymmetric synthesis from *ortho*-amino acetophenones[11] with substituted benzaldehydes. Recently Lee et.al[12] reported AgOTf catalyzed one-pot synthesis of *Ortho*-aminoacetophenone with the aromatic aldehyde to accomplish aza-flavanones. Nevertheless, methods to synthesize aza-flavanones suffer with long reaction time, low yields and expensive catalysts.[12] To overcome these challenges, we have developed an efficient metal-free, inexpensive TsOH catalytic systems to synthesize a variety of aza-flavanones in good yields and evaluated their*in vitro* inhibitory activity against α-glucosidase.

2. Results and discussions

2.1 Chemistry

We have taken 1-(2-aminophenyl)-3-hydroxyhexan-1-one (**4a)** as a model substrate for this reaction, which was readily prepared from 2-nitroacetophenone (Scheme 1).[13] Aldol reaction of 2-nitroacetophenone with various aldehydes furnished alcohols **2a-w** in moderate yields (48-69%) along with the enones**3a-w** (8-15%). Isolation of alcohols **2a-w** and subsequent reduction afforded suitable substrates **4a-w** in good yield (78-91%).



Scheme 1. Reagents and conditions: (i) RCHO (1.1 equiv), LDA (2.5 equiv), THF, -78 °C, 1 h, 48-69% (ii) 10% Pd/C (20% wt), EtOH, 50 psi, 1 h, 78-91%

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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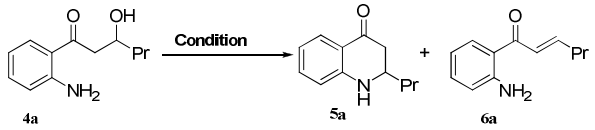
Once the substrate **4a** was synthesized, we investigated our attempts with several Lewis and Bronsted acids for the reaction, in which desired aza-flavanone **5a** and enone **6a** were formed in different ratios (Table 1). The reaction was unsuccessful (starting material was recovered) in the absence of a catalyst, even after heating at 120 °C for 12 h in toluene. Initially we have screened with 10mol% and 30mol% of catalyst. In both conditions we observed reactions were very sluggish and no progress after 16 h. It is observed that 50 mol% of catalyst is necessary in order to achieve complete conversion. It was gratifying to note that the conversion is clean and required product **5a** was isolated in 90% yield in the presence of TsOH (without formation of side product **6a**). Surprisingly, Amberlyst and Dowex afforded the desired compound almost in quantitative yields. These catalysts can be easily recovered and reused without loss of activity.

Table 1. Optimization of reaction condition for the synthesis of 5a[a]



4a 5a 6a

Entry	Condition	5a (%)	6a (%)
1	No catalyst	0	0
2	H_3PO_4	28	36
3	$AlCl_3$	37	48
4	$FeCl_3$	52	18
5	TfOH	78	10
6	$ZnCl_2$	74	5
7	TsOH	90	0
8	Amberlyst	97	0
9	Dowex	98	0

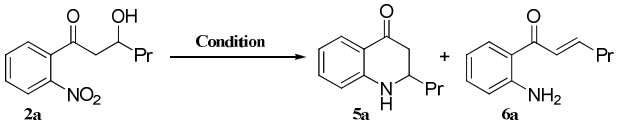
[a] Catalyst (0.5 equiv), toluene, 120 °C, 1-2 h

In addition, we extended the scope of the reaction to heterocycles attached to hydroxy bearing carbon (**4m-u**). Attempts to synthesize pyridine substituted aza-flavanones (**5m-o**) either using our catalytic system or Amberlyst and Dowex catalytic systems were futile, whereas the reaction was successful when 0.75 equiv of $ZnCl_2$ was employed.

Inspired by the results, the reaction was explored with various substrates and synthesized a library of aza-flavanones. To generalise the synthetic approach a long range of examples were synthesized adopting this methodology using simple nitroacetophenone with different aldehydes (aliphatic, aromatic (with electron donating & withdrawing), hetero aromatic (five membered and six membered)) and substituted nitroacetophenone (electron donating & withdrawing functionality on phenyl ring)with valeraldehyde, products are tabulated in Table 3.

For the nitro reduction of 3-(4-Bromophenyl)-3-hydroxy-1-(2-nitrophenyl)propan-1-one (**2f**), avoided Pd/C (because of bromo group) attempted Fe/AcOH. Surprisingly 56% of 2-(4-bromophenyl)-2,3-dihydroquinolin-4(1H)-one (**5f**) final compound isolated. The result was encouraging hence we have explored one pot cyclization of **2a** using the variety of reducing agents. The best result was obtained when Fe/AcOH was employed which afforded **5a** directly (58% yield) with enone **6a** (12% yield) (Table 2). The side product enone was increased when other reducing agents were used such as Fe/TsOH and Zn/AcOH. Eventually even with isolated **6a** under optimized condition yielded the desired product **5a** in good yields. We have attempted metal (Iron, Pd/Cyclohexene) with polymer acid resins (Amberlyst and Dowex) all attempts were unsuccessful.

Table 2. One-pot cyclization[b]



2a 5a 6a

Entry	Condition	5a (%)	6a (%)
1	Fe/AcOH	58	12
2	Fe/TsOH	26	32
3	Zn/AcOH	28	40
4[c]	$SnCl_2$/AcOH	35	28
5[c]	Pd/HCO_2NH_4	45	24

[b] Metal (1.0 equiv), Acid (3.0 equiv), toluene, 120 °C, 6 h
[c] EtOH used as solvent

2.2. Biology

Next, we have subjected twenty compounds to evaluate their α-glucosidase inhibitory activity in comparison to Acarbose, Miglitol and Voglibose as reference standards and Baker's yeast α-glucosidase inhibitory activity was assayed using the reported method.[14] The IC_{50} (best fit) were calculated using graph pad prism v 6.0 where n=3 and results are tabulated in Table-4. It is evident from the results that many of aza-flavanone derivatives showed promising inhibitory activity. Among the aliphatic derivatives acyclic aza-flavanone derivatives (**5a** and **5c**) exhibited high α-glucosidase activity compared to alicyclic derivatives (**5b** and **5d**). Simple phenyl ring containing aza-flavanone derivative (**5e**) has shown negligible α-glucosidase activity. An enormous variation was observed when phenyl ring is substituted with electron withdrawing group having phenyl ring like 4-trifluoromethyl phenyl derivative (**5g**) showed 6-8 fold higher α-glucosidase activity with an IC_{50} of 53.52 µM compared to standard references, 2,4-difluoro phenyl derivative (**5h**) also showed significant inhibition activity. The enzyme inhibition activity was decreased when phenyl ring was replaced with electron rich phenyl rings like methoxyphenyl derivative (**5i**) or 3, 4-dimethyl phenyl derivative (**5l**).

Among heterocyclic derivatives, compounds containing pyridine scaffolds (**5n** and **5o**) have shown low inhibition activity compared to furan and thiophene derivatives. 3-Furan derivative (**5p**) exhibited better activity compared to the corresponding reduced derivative 3-tetrahydrofuran (**5t**). Among all the heterocyclic derivatives promising activity was observed in 3-thiophene derivative (**5r**) with an IC_{50} of 72.39 µM. Results clearly indicated that 3-substitueted aromatic five- membered heterocyclic rings (**5p**, **5r**) are more potent than 2-substituted derivatives (**5q**, **5s**). Flurodihydroquinolinone derivative (**5w**) with an IC_{50} of 133.8 µM showed high inhibition activity compared to methoxydihydroquinolinone derivative (**5v**) with an IC_{50} of 683.2 µM.

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3. Molecular Modeling

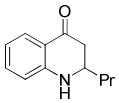
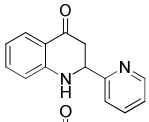
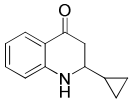
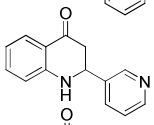
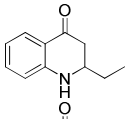
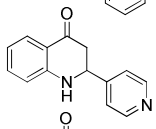
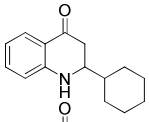
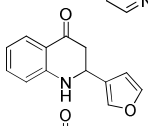
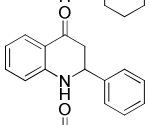
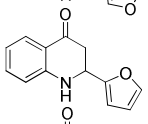
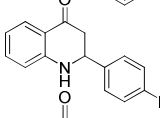
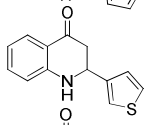
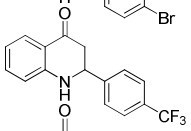
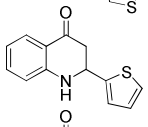
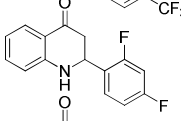
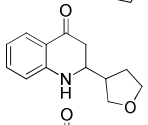
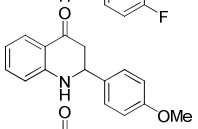
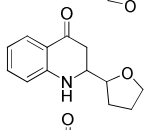
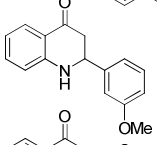
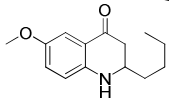
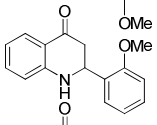
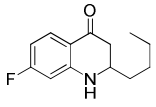
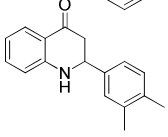
To find some structural insight into the inhibitory mechanisms of the identified inhibitors of α-glucosidase, their binding modes in the active site were investigated using the Meastro 9.7 in Schrödinger software.[15]

3.1. Homology modeling of α-glucosidase

To the best of our knowledge, the crystal structure for α-glucosidase of *Saccharomyces cerevisiae* (Baker's *yeast)* has not been reported yet. So, we developed the three dimensional (3D) model for α-glucosidase of *S. cerevisiae* by a comparative modelling technique. The homology model of *S. cerevisiae* α-glucosidase was built with Prime 3.5 in Schrödinger software.

The protein sequence of *S. cerevisiae* α-glucosidase was downloaded from the universal protein resource (Uniprot, Entry Id: P53341). Template search was performed using Blast Homology-Search tools against the PDB databank implemented in Prime 3.5. The crystallographic structure of *Saccharomyces cerevisiae* isomaltase (PDB ID: 3A4A, 1.6 Å resolution) [16] with 72% of identity and 85% similar sequence with the target was selected as the template. Three dimensional (3D) model of yeast α-glucosidase was built using Prime homology modeling tools. The modeled 3D structure was evaluated with the help of Ramchandran plot and protein reports.

Table 3. Substrate scope

Cpd No	Product	Condition	Yield	Cpd No	Product	Condition	Yield
5a		a	90%	**5m**		b	51%
5b		a	85%	**5n**		b	48%
5c		a	85%	**5o**		b	55%
5d		a	80%	**5p**		a	71%
5e		a	74%	**5q**		a	62%
5f		a	54%	**5r**		a	72%
5g		a	60%	**5s**		a	74%
5h		a	68%	**5t**		a	76%
5i		a	74%	**5u**		a	69%
5j		a	70%	**5v**		a	76%
5k		a	72%	**5w**		a	73%
5l		a	65%				

a TsOH (0.5 equiv), toluene, 120 °C, 1-2 h
b $ZnCl_2$ (0.75 equiv), toluene, 120 °C, 1-2 h

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Table 4.α-Glucosidase inhibitory activity of aza-flavanones

Compound No	Alpha Glucosidase inhibition IC_{50} (μM)	Compound No	Alpha Glucosidase inhibition IC_{50} (μM)
5a	189.7	5p	352.1
5b	283.8	5q	486.7
5c	271.6	5r	72.39
5d	494.4	5s	381.8
5e	685.6	5t	866.9
5f	SI	5u	667.1
5g	53.52	5v	683.2
5h	210.6	5w	133.8
5i	302.8	**Acarbose**	**360.2**
5l	606.2	**Voglibose**	**324.7**
5n	NI	**Miglitol**	**462.2**
5o	772.7		

SI: Solubility issue, NI: Not identified

Figure 1shows the homology-modeled structure of α-glucosidase and its Ramchandran plot. Figure S1 (Supplementary material) displays the sequence alignment between α-glucosidase from *S. cerevisiae* and isomaltase from *S. cerevisiae* (PDB ID: 3A4A). Ramchandran plot analysis of the yeast α-glucosidase structure showed that >95% residues are favored and allowed ϕ, ψ backbone conformational regions (Figure S2, Supplementary material). Visualization and characterization of the catalytic binding site was done using the SiteMap module of Meastro 9.7.

3.2. Molecular docking simulations and *binding energy calculations*

The molecular docking study was carried out to explore the binding mode of synthesized aza-flavanones within the binding pocket of α-glucosidase using Glide 6.2 in Schrödinger software. Docking procedure was followed using the standard protocol implemented in Maestro 9.7 and the compounds were docked against three dimensional homology model of α-glucosidase. As a means of validation of the docking protocol, the known inhibitor Acarbose was docked into the binding pocket of a developed homology model, the Acarbose accommodates well in the binding pocket and showed interaction to the important active site residues (Figure S3, Supplementary material).

All the compounds were docked into the binding pocket of a developed homology model of α-glucosidase enzyme. Table 5 (Supplementary material) demonstrates the result of the molecular docking along with hydrogen bonding as well as arene-arene interactions of compounds with α-glucosidase enzyme. Based on the docking scores and the experimental IC_{50} values, we have performed MM/GBSA binding energy calculations of complexes between compounds and glucosidase enzyme (Table 6-supplementary material). From these molecular modeling studies it was observed that the top ranked conformation of the most active compound **5g** (Figure 2) established four hydrogen bonds between the carbonyl group on aza-flavanone ring of the compound and the active site residues (Lys 153, Arg 312, Tyr 313, Asn 412) with binding energy of 48.60 kcal/mol.

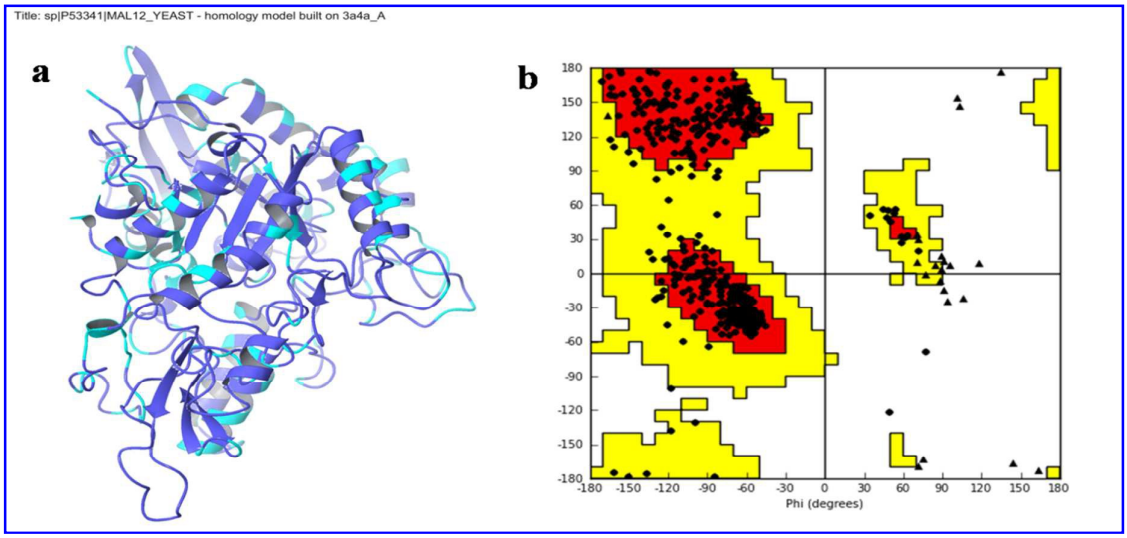

Figure 1. a) Graphic representation of the homology modeling structure of α-glucosidase from *S. cerevisiae*. b) Ramachandran plot for the modeled α-glucosidase of *S. cerevisiae*. The plot is organized as follows: Glycine, proline and all other residues are plotted as triangles, squares, and circles respectively. The red, yellow and white regions represent the favoured, allowed and the disallowed regions respectively.

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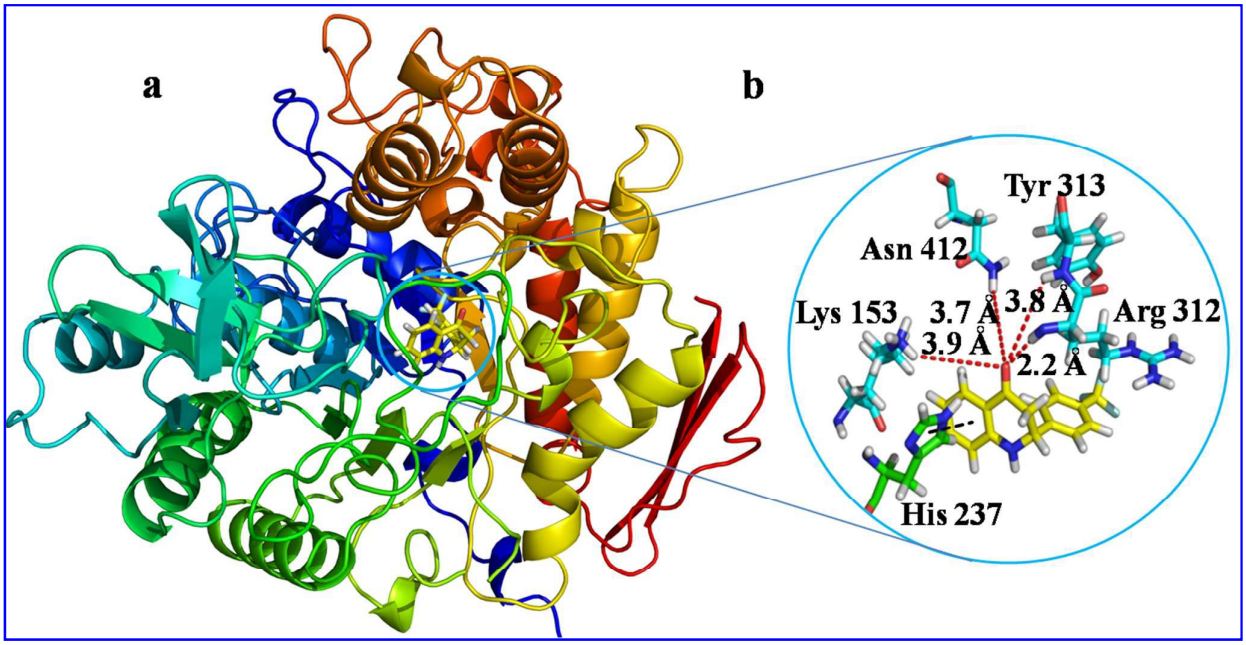

Figure 2.a) Docking of the most active compound **5g** (yellow colour stick) and b) its ligand-protein interactions in the binding site of modeled α-glucosidase. The red dashed lines represent hydrogen bonds. H-bond distances (in Å) between heteroatoms of ligand and amino acid residues are as follows: Lys 153 (3.9), Arg 312 (2.2), Tyr 313 (3.8), Asn 412 (3.7). The black dashed line indicates arene-arene interaction with His 237.

Additionally the aryl group of the compound formed a **π - π** stacking interaction (arene-arene interaction) with the His 237. Furthermore, several hydrophobic interactions were observed between the compound **5g** and the active site residues, e.g., Phe 155, Phe 156, Leu 174, Phe 175, Leu 216, Pro 238, Ala 276, Phe 300, Val 303, Pro 309, Phe 310, Phe 311 and Tyr 313 are the other residues that stabilized the binding of the compound **5g** in the active site of α-glucosidase. Similar interactions were found in compound **5r** (binding energy= -43.69kcal/mol) with residues Lys 153, Arg 312, Tyr 313 and Asn 412, these interactions made this compound second active compound in the series. The strong hydrogen bonding network observed for compounds **5g, 5r, 5w, 5h** and **5a** by the carbonyl group attached to the aza-flavanone ring. The good biological activity of compounds **5g, 5w** and **5h** might be due to the presence of fluoro groups; particularly trifluoromethyl group in compound **5g**, the trifluoromethyl moiety has strong electron withdrawing inductive effect. This effect of trifluoromethyl moiety might increases the ability of interactions with catalytic site residues, that might be one of the reasons for its highest activity showed in the series. Similarly, Compound **5w** and **5a** also exhibited the good biological activities against the enzyme, but if compare the compound **5w** with **5a**, it is found that **5w** has more biological activity, docking score and more protein-ligand interactions because of presence of both electron withdrawing group and aliphatic side chain. These observations can be verified in case of compounds **5i** to **5l** as they have low biological activities as well as less docking score and interaction with active site residue as compared to compound **5g**. As these compounds have groups with electron donating effect instead of fluoro group present as in compounds **5g, 5h** and **5w**. Similarly other less active compounds lacking the electron withdrawing group that makes them slightly less active as compare to compound **5g**. From the docking study it was observed that the presence of carbonyl group responsible for strong hydrogen bonding, presence arene moiety in basic scaffold of aza-flavanone is helpful in establishing **π – π** stacking and finally substitutions over second position of aza-flavanone system is supportive in hydrophobic interactions.Thus, molecular modeling studies were performed on azaflavanones had provided us with some good results, which best explain the compounds *in vitro* **α**-glucosidase inhibitory activity.

4. Experimental

4.1. Chemistry

Melting points were determined in capillaries, recorded on Buchi Melting Point B-540and are uncorrected. IR data was recorded on Perkin Elmer Spectrum 100. ^{1}H and ^{13}CNMR spectra were recorded on Varian 400 MHz and 300 MHz spectrometers, using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts are given in ppm with TMS as an internal reference. J values are given in Hertz. Reactions were monitored by thin-layer chromatography (TLC) coated with Silica Gel. Column chromatography was performed with 100-200 mesh silica.

4.1.1. General procedure for the preparation of compounds 2a-w

To a cooled solution of diisopropylamine (3.0 eq) at -78 °C in THF (20 vol) was added *n*-BuLi (2.5 eq, 1.0 M solution in hexane). After addition of *n*-BuLi, the reaction mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. To this solution was added drop-wise nitroacetophenone (1.0 eq). The reaction mixture was stirred at -78 °C for 20 min and to this solution was added a solution of aldehyde derivative (1.1 eq) in THF (5 vol). The reaction mixture was stirred for 1 h at -78 °C and was quenched with a saturated NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The organic phase was combined and

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dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography to give compound **2a-w** (48-69 %).

4.1.1.1. 3-Hydroxy-1-(2-nitrophenyl)hexan-1-one (2a):
Yield: 63%;IR (KBr, cm^{-1}): 3436 (OH), 1654 (CO), 1530 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.2Hz, 1H), 7.74 (t, J = 7.6Hz, 1H), 7.62 (t, J = 7.6Hz, 1H), 7.44 (dd, J = 1.2, 7.6Hz, 1H), 4.32-4.28 (m, br, 1H), 3.16 (dd, J = 2.6, 17.2Hz, 1H), 2.89-2.83 (m, 1H), 1.59-1.38 (m, 4H), 0.95 (t, J = 6.8Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.23, 137.62, 134.38, 130.67, 127.37, 124.41, 124.02, 67.79, 49.62, 38.61, 18.62, 13.92; LC-MS (ESI): m/z Calcd. for $C_{12}H_{15}NO_4$: 237.10, Found 238.01 $[M+H]^+$

4.1.1.2. 3-Cyclopropyl-3-hydroxy-1-(2-nitrophenyl)propan-1-one (2b):
Yield: 68%;IR (KBr, cm^{-1}): 3431 (OH), 1689 (CO), 1560 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.4Hz, 1H), 7.74 (t, J = 7.6Hz, 1H), 7.62 (t, J = 9.0Hz, 1H), 7.47 (dd, J = 1.2, 7.6Hz, 1H), 3.54 (t, J = 8.4Hz, 1H), 3.19-3.02 (m, 2H), 2.80 (s, br, OH, 1H), 1.04-0.95 (m, 1H), 0.63-0.49 (m, 2H), 0.46-0.40 (m, 1H), 0.30-0.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.71, 145.54, 137.68, 134.33, 130.63, 127.51, 124.32, 72.85, 49.52, 16.99, 3.35, 2.24;

4.1.1.3. 3-Hydroxy-1-(2-nitrophenyl)pentan-1-one (2c):
Yield: 62%;IR (KBr, cm^{-1}): 3432 (OH), 1689 (CO), 1525 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J = 0.8, 8.4Hz, 1H), 7.74 (t, J = 8.0Hz, 1H), 7.62 (t, J = 8.4Hz, 1H), 7.45 (dd, J = 1.6, 8.0Hz, 1H), 4.22-4.18 (m, br, 1H), 3.01 (dd, J = 2.4, 17.2Hz, 1H), 2.90-2.83 (m, 2H), 1.60-1.53 (m, 2H), 0.98 (t, J = 7.6Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.15, 145.54, 137.64, 134.37, 130.67, 127.41, 124.40, 69.38, 49.20, 29.45, 9.76; LC-MS (ESI): m/z Calcd. for $C_{11}H_{13}NO_4$: 223.08, Found 223.91 $[M+H]^+$

4.1.1.4. 3-Cyclohexyl-3-hydroxy-1-(2-nitrophenyl)propan-1-one (2d):
Yield: 59%;IR (KBr, cm^{-1}): 3434 (OH), 1703 (CO), 1538 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J = 0.8, 10.8Hz, 1H), 7.73 (td, J = 1.2, 10.0Hz, 1H), 7.61 (td, J = 1.6, 10.8Hz, 1H), 7.45 (dd, J = 1.6, 10.0Hz, 1H), 4.07-4.03 (m, 1H), 3.05-2.99 (m, 1H), 2.91-2.56 (m, 2H), 1.87-1.66 (m, 4H), 1.48-1.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.63, 145.48, 137.79, 134.34, 130.59, 127.45, 124.34, 72.13, 46.93, 43.11, 28.81, 28.04, 26.35, 26.09, 25.99; LC-MS (ESI): m/z Calcd. for $C_{15}H_{19}NO_4$: 277.13, Found 278.22 $[M+H]^+$

4.1.1.5. 3-Hydroxy-1-(2-nitrophenyl)-3-phenylpropan-1-one (2e):
Yield: 64%;MR: 85-88 °C; IR (KBr, cm^{-1}): 3445 (OH), 1703 (CO), 1560 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 7.2Hz, 1H), 7.72 (t, J = 8.0Hz, 1H), 7.61 (t, J = 8.0Hz, 1H), 7.41-7.26 (m, 6H), 5.42-5.39 (m, 1H), 3.24-3.20 (m, 2H); LC-MS (ESI): m/z Calcd. for $C_{15}H_{13}NO_4$: 271.08, Found NO mass ionization

4.1.1.6. 3-(4-Bromophenyl)-3-hydroxy-1-(2-nitrophenyl)propan-1-one (2f):
Yield: 54%;IR (KBr, cm^{-1}): 3476 (OH), 1688 (CO), 1539 (NO_2); ^1H NMR (300 MHz, $CDCl_3$): δ 8.14 (dd, J = 1.2, 8.1Hz, 1H), 7.74 (t, J = 7.8Hz, 1H), 7.63 (t, J = 8.1Hz, 1H), 7.49-7.39 (m, 3H), 7.32-7.26 (m, 2H), 5.40-5.37 (m br, 1H), 3.26 (d, J = 3.0Hz, 1H), 3.15-3.13 (m, 2H); LC-MS (ESI): m/z Calcd. for $C_{15}H_{12}BrNO_4$: 348.99, Found 374.5 $[M+Na]^+$

4.1.1.7. 3-Hydroxy-1-(2-nitrophenyl)-3-(4-(trifluoromethyl)phenyl)propan-1-one (2g):
Yield: 52%;IR (KBr, cm^{-1}): 3427 (OH), 1701 (CO), 1530 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, J = 0.8, 8.0Hz, 1H), 7.73 (td, J = 1.2, 7.8Hz, 1H), 7.65-7.26 (m, 3H), 7.54-7.47 (m, 2H), 7.40 (dd, J = 1.2, 7.2Hz, 1H), 5.48 (dd, J = 3.2, 8.8Hz, 1H), 3.38 (s, OH, 1H), 3.18-3.15 (m, 2H); LC-MS (ESI): m/z Calcd. for $C_{16}H_{12}F_3NO_4$: 339.07, Found NO mass ionization

4.1.1.8. 3-(2,4-Difluorophenyl)-3-hydroxy-1-(2-nitrophenyl)propan-1-one (2h):
Yield: 54%;MR: 77-75 °C; IR (KBr, cm^{-1}): 3368 (OH), 1655 (CO), 1525 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, J = 1.2, 8.4Hz, 1H), 7.74 (td, J = 1.2, 7.4Hz, 1H), 7.63 (td, J = 1.2, 8.4Hz, 1H), 7.58-7.52 (m, 1H), 7.43 (dd, J = 1.6, 8.0Hz, 1H), 6.90 (td, J = 2.0, 8.0Hz, 1H), 6.78 (td, J = 1.2, 8.4Hz, 1H), 5.62 (dd, J = 2.0, 8.8Hz, 1H), 3.28-3.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.22, 162.35 (dd), 159.36 (dd), 145.50, 137.05, 134.42, 130.93, 128.43-128.37 (m), 127.31, 125.33 (d), 124.47, 111.44 (dd), 103.71 (t), 64.31, 49.94; LC-MS (ESI): m/z Calcd. for $C_{15}H_{11}F_2NO_4$: 299.12, Found NO mass ionization

4.1.1.9. 3-Hydroxy-3-(4-methoxyphenyl)-1-(2-nitrophenyl)propan-1-one (2i):
Yield: 61%;IR (KBr, cm^{-1}): 3458 (OH), 1615 (CO), 1542 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J = 1.2, 10.8Hz, 1H), 7.72 (t, J = 8.0Hz, 1H), 7.61 (t, J = 8.4Hz, 1H), 7.41 (dd, J = 1.2, 8.8Hz, 1H), 7.32 (d, J = 8.4Hz, 2H), 6.88 (d, J = 12.0Hz, 2H), 5.35-5.32 (m, 1H), 3.79 (s, 3H), 3.19-3.16 (m, 2H), 3.06 (s, br, OH, 1H); LC-MS (ESI): m/z Calcd. for $C_{16}H_{15}NO_5$: 301.10, Found 324 $[M+Na]^+$

4.1.1.10. 3-Hydroxy-3-(3-methoxyphenyl)-1-(2-nitrophenyl)propan-1-one (2j):
Yield: 60%;IR (KBr, cm^{-1}): 3467 (OH), 1703 (CO), 1545 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 7.6Hz, 1H), 7.72 (d, J = 8.4Hz, 1H), 7.61 (t, J = 8.0Hz, 1H), 7.41 (d, J = 8.0Hz, 1H), 7.26 (t, J = 6.0Hz, 1H), 6.96 (d, J = 7.6Hz, 2H), 6.81 (d, J = 8.4Hz, 1H), 5.36 (t, J = 5.6Hz, 1H), 3.81 (s, 3H), 3.18 (d, J = 6.0Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.29, 159.85, 145.45, 144.14, 137.47, 134.38, 130.77, 129.64, 127.45, 124.38, 117.88, 113.48, 111.04, 70.33, 55.25, 51.68; LC-MS (ESI): m/z Calcd. for $C_{16}H_{15}NO_5$: 301.10, Found 300.4 $[M-H]^-$

4.1.1.11. 3-Hydroxy-3-(2-methoxyphenyl)-1-(2-nitrophenyl)propan-1-one (2k):
Yield: 58%;MR: 85-88 °C; IR (KBr, cm^{-1}): 3492 (OH), 1688 (CO), 1518 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.4Hz, 1H), 7.70 (t, J = 8.4Hz, 1H), 7.59 (t, J = 8.4Hz, 1H), 7.44 (t, J = 8.0Hz, 2H), 7.25 (t, J = 8.4Hz, 1H), 6.97 (t, J = 7.2Hz, 1H), 6.85 (d, J = 8.4Hz, 1H), 5.57-5.52 (m, 1H), 3.83 (s, 3H), 3.36-3.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.45, 155.93, 145.76, 137.66, 134.21, 130.58, 130.44, 128.62, 127.72, 126.47, 124.24, 120.82, 110.28, 66.56, 55.24, 49.79; LC-MS (ESI): m/z Calcd. for $C_{16}H_{15}NO_5$: 301.10, Found 324.61$[M+Na]^+$

4.1.1.12. 3-(3,4-Dimethylphenyl)-3-hydroxy-1-(2-nitrophenyl)propan-1-one (2l):
Yield: 63%;MR: 82-85 °C; IR (KBr, cm^{-1}): 3429 (OH), 1689 (CO), 1529 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J = 0.9, 8.1Hz, 1H), 7.72 (t, J = 6.6Hz, 1H), 7.62 (t, J = 9.0Hz, 1H), 7.42 (dd, J = 1.5, 7.5Hz, 1H), 7.17 (s, br, 1H), 7.11 (s, br, 2H), 5.35-5.31 (m, 1H), 3.40-3.17 (m, 2H), 2.25 (d, J = 3.9Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.38, 145.55, 139.93, 137.58, 136.82, 136.21, 134.33, 130.68, 129.78, 127.50, 126.91, 124.34, 123.05, 70.31, 51.66, 19.74, 19.40; LC-MS (ESI): m/z Calcd. for $C_{17}H_{17}NO_4$: 299.12, Found NO mass ionization

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4.1.1.13. 3-Hydroxy-1-(2-nitrophenyl)-3-(pyridin-2-yl)propan-1-one (2m):

Yield: 48%;IR (KBr, cm^{-1}): 3392 (OH), 1704 (CO), 1528 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.53-8.51 (m, 1H), 8.10 (d, *J* = 8.4Hz, 1H), 7.72 (t, *J* = 7.6Hz, 2H), 7.60 (t, *J* = 8.0Hz, 1H), 7.53-7.47 (m, 2H), 7.24-7.20 (m, 1H), 5.38 (dd, *J* = 3.6, 8.8Hz, 1H), 3.71-3.58 (m, 1H), 3.44 (dd, *J* = 4.0, 12.6Hz, 1H), 3.28-3.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.74, 160.38, 148.40, 136.98, 134.30, 130.59, 127.79, 124.23, 123.19, 122.99, 122.67, 120.60, 69.85, 50.45; LC-MS (ESI): m/z Calcd. for $C_{14}H_{12}N_2O_4$: 272.08, Found 273.31 $[M+H]^+$

4.1.1.14. 3-Hydroxy-1-(2-nitrophenyl)-3-(pyridin-3-yl)propan-1-one (2n):

Yield: 51%;IR (KBr, cm^{-1}): 3435 (OH), 1663 (CO), 1531 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, *J* = 2.0Hz, 1H), 8.54 (dd, *J* = 1.2, 4.8Hz, 1H), 8.15 (d, *J* = 8.0Hz, 1H), 7.78-7.73 (m, 2H), 7.64 (t, *J* = 8.4Hz, 1H), 7.42 (dd, *J* = 1.2, 7.2Hz, 1H), 7.31-7.27 (m, 1H), 5.47 (t, *J* = 6.8Hz, 1H), 3.20 (d, *J* = 6.8Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.04, 150.08, 149.09, 147.81, 137.98, 137.19, 134.48, 133.61, 130.95, 127.38, 124.50, 123.51, 68.22, 51.32; LC-MS (ESI): m/z Calcd. for $C_{14}H_{12}N_2O_4$: 272.08, Found 273.06 $[M+H]^+$

4.1.1.15. 3-Hydroxy-1-(2-nitrophenyl)-3-(pyridin-4-yl)propan-1-one (2o):

Yield: 55%;IR (KBr, cm^{-1}): 3392 (OH), 1704 (CO), 1528 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 5.2Hz, 2H), 8.14 (d, *J* = 8.0Hz, 1H), 7.75 (t, *J* = 7.6Hz, 1H), 7.64 (t, *J* = 7.2Hz, 1H), 7.43 (dd, *J* = 1.2, 7.6Hz, 1H), 7.34 (d, *J* = 6.0Hz, 2H), 5.42 (dd, *J* = 3.2, 8.8Hz, 1H), 3.23-3.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.72, 151.66, 149.77, 145.39, 137.13, 134.55, 130.96, 127.31, 124.48, 120.61, 68.75, 51.12; LC-MS (ESI): m/z Calcd. for $C_{14}H_{12}N_2O_4$: 272.08, Found 273.13

4.1.1.16. 3-(Furan-3-yl)-3-hydroxy-1-(2-nitrophenyl)propan-1-one (2p):

Yield: 65%;IR (KBr, cm^{-1}): 3421 (OH), 1703 (CO), 1527 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.0Hz, 1H), 7.72 (t, *J* = 8.4Hz, 1H), 7.62 (t, *J* = 8.4Hz, 1H), 7.44-7.42 (m, 2H), 7.38-7.37 (m, 1H), 6.40 (s, 1H), 5.38-5.34 (m, br, 1H), 3.22-3.21 (m, 2H), 3.07 (d, *J* = 3.6Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 202.01, 145.56, 143.45, 139.10, 137.37, 134.36, 130.78, 127.42, 127.27, 124.40, 108.34, 63.45, 50.33; LC-MS (ESI): m/z Calcd. for $C_{13}H_{11}NO_5$: 261.06, Found 284.00 $[M+Na]^+$

4.1.1.17. 3-(Furan-2-yl)-3-hydroxy-1-(2-nitrophenyl)propan-1-one (2q):

Yield: 62%;IR (KBr, cm^{-1}): 3429 (OH), 1702 (CO), 1526 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 1.2, 8.0Hz, 1H), 7.73 (t, *J* = 8.0Hz, 1H), 7.62 (t, *J* = 8.0Hz, 1H), 7.43 (dd, *J* = 1.2, 7.6Hz, 1H), 7.35 (s, 1H), 6.34-6.31 (m, 2H), 5.39-5.36 (m, 1H), 3.39-3.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.49, 154.51, 145.49, 142.24, 137.35, 134.36, 130.80, 127.49, 124.40, 110.34, 106.63, 64.16, 47.91; LC-MS (ESI): m/z Calcd. for $C_{13}H_{11}NO_5$: 261.06, Found 262.27 $[M+H]^+$

4.1.1.18. 3-Hydroxy-1-(2-nitrophenyl)-3-(thiophen-3-yl)propan-1-one (2r):

Yield: 65%; IR (KBr, cm^{-1}): 3491 (OH), 1711 (CO), 1525 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 1.2, 8.4Hz, 1H), 7.73 (t, *J* = 7.6Hz, 1H), 7.62 (t, *J* = 8.4Hz, 1H), 7.40 (dd, *J* = 1.6, 7.6Hz, 1H), 7.31-7.29 (m, 1H), 7.27-7.26 (m, 1H), 7.08 (dd, *J* = 1.6, 5.2Hz, 1H), 5.48 (t, *J* = 5.2Hz, 1H), 3.24 (d, *J* = 7.6Hz, 2H), 3.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.24, 145.45, 143.71, 137.40, 134.44, 130.79, 127.41, 126.40, 125.36, 124.40, 121.09, 66.83, 50.85; LC-MS (ESI): m/z Calcd. for $C_{13}H_{11}NO_4S$: 277.04, Found No ionization

4.1.1.19. 3-Hydroxy-1-(2-nitrophenyl)-3-(thiophen-2-yl)propan-1-one (2s):

Yield: 67%;IR (KBr, cm^{-1}): 3445 (OH), 1703 (CO), 1527 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 0.8, 8.0Hz, 1H), 7.73 (t, *J* = 1.2, 7.8Hz, 1H), 7.62 (t, *J* = 1.2, 8.0Hz, 1H), 7.41 (dd, *J* = 1.2, 7.8Hz, 1H), 7.25 (dd, *J* = 1.2, 7.8Hz, 1H), 7.01 (d, *J* = 3.2Hz, 1H), 6.96 (t, *J* = 5.2Hz, 1H), 5.64 (t, *J* = 5.6Hz, 1H), 3.33 (d, *J* = 6.0Hz, 2H), 3.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.59, 146.09, 145.54, 137.30, 134.37, 130.81, 127.43, 126.71, 124.90, 124.40, 123.84, 66.64, 51.53; LC-MS (ESI): m/z Calcd. for $C_{13}H_{11}NO_4S$: 277.04, Found No ionization

4.1.1.20. 3-Hydroxy-1-(5-methoxy-2-nitrophenyl)heptan-1-one (2v):

Yield: 59%;IR (KBr, cm^{-1}): 3288 (OH), 1647 (CO), 1503 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4Hz, 1H), 7.42 (d, *J* = 2.8Hz, 1H), 7.15 (dd, *J* = 2.4, 8.8Hz, 1H), 6.61 (s, 1H), 4.18-4.10 (m, br, 1H), 3.91 (s, 3H), 3.24-3.20 (m, 2H), 1.54-1.25 (m, 6H), 0.94-0.89 (m, 3H); LC-MS (ESI): m/z Calcd. for $C_{14}H_{19}NO_5$: 281.13, Found 281.95 $[M+H]^+$

4.1.1.21. 1-(4-Fluoro-2-nitrophenyl)-3-hydroxyheptan-1-one (2w):

Yield: 52%;IR (KBr, cm^{-1}): 3098 (OH), 1708 (CO), 1539 (NO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (dd, *J* = 2.4, 8.0Hz, 1H), 7.50-7.41 (m, 2H), 4.23 (s, br, 1H), 2.97 (dd, *J* = 2.4, 17.2Hz, 1H), 2.89-2.82 (m, 1H), 2.67 (s, OH, 1H), 1.63-1.30 (m, 6H), 0.91 (t, *J* = 7.2Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.66, 162.64 (d), 146.92, 133.62, 129.52 (d), 121.34 (d), 112.16 (d), 68.14, 49.57, 36.31, 27.53, 22.52, 13.93; LC-MS (ESI): m/z Calcd. for $C_{13}H_{16}FNO_4$: 269.11, Found 269.96 $[M+H]^+$

4.1.2. General procedure for the preparation of compounds 4a-w

Compound **2** (1.0 eq) was taken in EtOH (10.0 Vol) and hydrogenated (3.5 bar H_2) over 10% palladium on charcoal (20 % wt). The reaction mixture was filtered through a pad of celite and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give compound **4a-w** (78-91 %)

4.1.2.1. 1-(2-Aminophenyl)-3-hydroxyhexan-1-one (4a):

Yield: 90%;IR (KBr, cm^{-1}): 3453 (OH), 3345 (NH_2), 1615 (CO); ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 1.5, 8.4Hz, 1H), 7.30-7.24 (m, 1H), 6.67-6.62 (m, 2H), 6.28 (s br, NH_2, 2H), 4.23-4.15 (m, br, 1H), 3.39 (s, OH, 1H), 3.15 (dd, *J* = 2.4, 17.1Hz, 1H), 3.02-2.93 (m, 1H), 1.64-1.41 (m, 4H), 0.96 (t, *J* = 7.5Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.05, 150.47, 134.72, 131.09, 117.82, 117.42, 115.87, 67.71, 45.25, 38.64, 18.79, 14.05; LC-MS (ESI): m/z Calcd. for $C_{12}H_{17}NO_2$: 207.13, Found 208.20 $[M+H]^+$

4.1.2.2. 1-(2-Aminophenyl)-3-cyclopropyl-3-hydroxypropan-1-one (4b):

Yield: 86%;IR (KBr, cm^{-1}): 3445 (OH), 3343 (NH_2), 1616 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.0Hz, 1H), 7.29-7.25 (m, 1H), 6.67-6.63 (m, 2H), 6.28 (s, br, NH_2, 2H), 3.45 (t, *J* = 8.8Hz, 1H), 3.33-3.16 (m, 2H), 1.03-0.99 (m, 1H), 0.63-0.42 (m, 3H), 0.24-0.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.68, 150.51, 134.71, 131.19, 117.84, 117.40, 115.80, 72.94, 45.36, 16.78, 3.43, 2.15; LC-MS (ESI): m/z Calcd. for $C_{12}H_{15}NO_2$: 205.11, Found 206.13 $[M+H]^+$

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4.1.2.3. 1-(2-Aminophenyl)-3-hydroxypentan-1-one (4c):
Yield: 88%;IR (KBr, cm^{-1}): 3433 (OH), 3385 (NH_2), 1660 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, J = 1.2, 8.4Hz, 1H), 7.29-7.27 (m, 1H), 6.66-6.62 (m, 2H), 6.27 (s br, NH_2, 2H), 4.20-4.05 (m, br, 1H), 3.35 (s, OH, 1H), 3.16 (dd, J = 2.8, 17.2Hz, 1H), 3.00-2.94 (m, 1H), 1.69-1.54 (m, 2H), 1.01 (t, J = 7.6Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.02, 150.51, 134.71, 131.12, 117.94, 117.44, 115.90, 64.42, 44.86, 29.41, 9.97;

4.1.2.4. 1-(2-Aminophenyl)-3-cyclohexyl-3-hydroxypropan-1-one (4d):
Yield: 85%;IR (KBr, cm^{-1}): 3468 (OH), 3886 (NH_2), 1614 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (dd, J = 1.6, 8.0Hz, 1H), 7.28-7.24 (m, 1H), 6.66-6.62 (m, 2H), 6.27 (s, br, NH_2, 2H), 3.97-3.93 (m, 1H), 3.17 (dd, J = 2.0, 17.2Hz, 1H), 3.01-2.94 (m, 1H), 1.94-1.91 (m, 1H), 1.80-1.67 (m, 4H), 1.50-1.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.41, 150.48, 134.65, 131.12, 118.04, 117.44, 115.87, 72.11, 43.14, 42.38, 29.05, 28.42, 26.53, 26.29, 26.18; LC-MS (ESI): m/z Calcd. for $C_{15}H_{21}NO_2$: 247.33, Found 248.21 $[M+H]^+$

4.1.2.5. 1-(2-Aminophenyl)-3-hydroxy-3-phenylpropan-1-one (4e):

Yield: 87%;IR (KBr, cm^{-1}): 3469 (OH), 3349 (NH_2), 1616 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (dd, J = 1.2, 8.1Hz, 1H), 7.45-7.24 (m, 6H), 6.66-6.58 (m, 2H), 6.32 (s br, NH_2, 2H), 5.31 (dd, J = 3.6, 8.1Hz, 1H), 3.34-3.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.09, 150.58, 143.07, 134.87, 131.08, 128.51, 127.56, 125.77, 117.53, 117.42, 115.90, 70.28, 47.62; LC-MS (ESI): m/z Calcd. for $C_{15}H_{15}NO_2$: 241.11, Found 264.18 $[M+Na]^+$

4.1.2.6. 1-(2-Aminophenyl)-3-hydroxy-3-(4-(trifluoromethyl)phenyl)propan-1-one (4g):
Yield: 79%;IR (KBr, cm^{-1}): 3391 (OH), 3326 (NH_2), 1619 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 7.60-7.49 (m, 4H), 7.08 (d, J = 9.6Hz, 2H), 6.75-6.63 (m, 2H), 5.18-5.02 (m, 2H), 2.52-2.46 (m, 1H), 2.12-2.04 (m, 1H); LC-MS (ESI): m/z Calcd. for $C_{16}H_{14}F_3NO_2$: 309.10, Found 310.11 $[M+H]^+$

4.1.2.7. 1-(2-Aminophenyl)-3-(2,4-difluorophenyl)-3-hydroxypropan-1-one (4h):
Yield: 82%;MR: 73-75 °C; IR (KBr, cm^{-1}): 3454 (OH), 3350 (NH_2), 1617 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 7.64-7.56 (m, 2H), 7.29-7.25 (m, 1H), 6.91 (td, J = 1.6, 8.0Hz, 1H), 6.79 (td, J = 2.4, 8.4Hz, 1H), 6.66-6.59 (m, 2H), 6.30 (s, br, NH_2, 2H), 5.53 (d, J = 9.2Hz, 1H), 3.98 (s, br, OH, 1H), 3.42 (dd, J = 2.4, 17.6Hz, 1H), 3.24-3.17 (m, 1H); LC-MS (ESI): m/z Calcd. for $C_{15}H_{13}F_2NO_2$: 277.09, Found 278.53 $[M+H]^+$

4.1.2.8. 1-(2-Aminophenyl)-3-hydroxy-3-(4-methoxyphenyl)propan-1-one (4i):
Yield: 85%;IR (KBr, cm^{-1}): 3444 (OH), 3278 (NH_2), 1614 (CO); ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (dd, J = 1.6, 10.8Hz, 1H), 7.37-7.26 (m, 3H), 6.92-6.87 (m, 2H), 6.66-6.61 (m, 2H), 6.31 (s, NH_2, 2H), 5.29-5.24 (m, 1H), 3.81 (s, 3H), 3.33-3.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.20, 159.07, 150.59, 135.32, 134.83, 131.11, 127.38, 117.64, 115.92, 114.05, 113.90, 69.95, 56.56, 47.60; LC-MS (ESI): m/z Calcd. for $C_{16}H_{17}NO_3$: 271.12, Found 294.16 $[M+Na]^+$

4.1.2.9. 1-(2-Aminophenyl)-3-hydroxy-3-(3-methoxyphenyl)propan-1-one (4j):
Yield: 81%;IR (KBr, cm^{-1}): 3468 (OH), 3976 (NH_2), 1614 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (dd, J = 1.6, 8.4Hz, 1H), 7.30-7.24 (m, 2H), 7.01-6.98 (m, 2H), 6.83 (dd, J = 1.6, 8.4Hz, 1H), 6.63-6.60 (m, 2H), 6.31 (s, NH_2, 2H), 5.28 (dd, J = 3.2, 8.8Hz, 1H), 3.82 (s, 3H), 3.33-3.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.04, 159.81, 150.60, 144.83, 134.86, 131.09, 129.52, 118.03, 117.57, 117.42, 115.91, 113.14, 111.22, 70.21, 55.23, 47.64; LC-MS (ESI): m/z Calcd. for $C_{16}H_{17}NO_3$: 271.12, Found 272.24 $[M+H]^+$

4.1.2.10. 1-(2-Aminophenyl)-3-hydroxy-3-(2-methoxyphenyl)propan-1-one (4k):
Yield: 84%;IR (KBr, cm^{-1}): 3465 (OH), 3382 (NH_2), 1614 (CO); ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (dd, J = 1.2, 8.1Hz, 1H), 7.56 (dd, J = 1.5, 7.2Hz, 1H), 7.29-7.24 (m, 2H), 7.01 (t, J = 6.9Hz, 1H), 6.88 (d, J = 8.1Hz, 1H), 6.67-6.58 (m, 2H), 5.57 (dd, J = 2.1, 9.0Hz, 1H), 3.84 (s, 3H), 3.53-3.47 (m, 1H), 3.21-3.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.66, 155.67, 150.52, 134.66, 131.28, 128.23, 126.47, 120.84, 117.81, 117.35, 115.82, 110.12, 109.95, 65.68, 55.24, 46.11; LC-MS (ESI): m/z Calcd. for $C_{16}H_{17}NO_3$: 271.12, Found 294.68 $[M+Na]^+$

4.1.2.11. 1-(2-Aminophenyl)-3-(3,4-dimethylphenyl)-3-hydroxypropan-1-one (4l):
Yield: 90%;IR (KBr, cm^{-1}): 3459 (OH), 1615 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 7.6Hz, 1H), 7.28-7.24 (m, 1H), 7.21 (s, 1H), 7.16-7.11 (m, 2H), 6.61-6.58 (m, 2H), 6.31 (s br, NH_2, 2H), 5.24 (dd, J = 3.6, 7.6Hz, 1H), 3.69 (s, OH, 1H), 3.32-3.30 (m, 2H), 2.27 (d, J = 7.6Hz, 6H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 202.22, 150.58, 140.60, 136.73, 135.88, 134.79, 131.12, 129.72, 127.06, 123.20, 117.66, 117.41, 115.90, 70.16, 47.70, 19.81, 19.43; LC-MS (ESI): m/z Calcd. for $C_{17}H_{19}NO_2$: 269.14, Found 270.23 $[M+H]^+$

4.1.2.12. 1-(2-Aminophenyl)-3-hydroxy-3-(pyridin-2-yl)propan-1-one (4m):
Yield: 83%;MR: 94-99 °C;IR (KBr, cm^{-1}): 3482 (OH), 3345 (NH_2), 1665 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 4.8Hz, 1H), 7.72-7.67 (m, 2H), 7.53 (d, J = 8.0Hz, 1H), 7.27-7.17 (m, 2H), 6.64-6.58 (m, 2H), 6.29 (s NH_2, 2H), 5.36 (dd, J = 2.8, 8.4Hz, 1H), 4.38 (s OH, 1H), 3.58 (dd, J = 3.2, 16.8Hz, 1H), 3.42-3.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.72, 161.84, 150.53, 148.54, 136.73, 134.67, 131.35, 122.28, 120.41, 117.85, 117.30, 115.85, 70.49, 46.32; LC-MS (ESI): m/z Calcd. for $C_{14}H_{14}N_2O_2$: 242.11, Found NO mass ionization

4.1.2.13. 1-(2-Aminophenyl)-3-hydroxy-3-(pyridin-3-yl)propan-1-one (4n):
Yield: 80%;IR (KBr, cm^{-1}): 3465 (OH), 3387 (NH_2), 1608 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.55 (d, J = 3.2Hz, 1H), 7.80 (d, J = 8.0Hz, 1H), 7.63 (d, J = 7.6Hz, 1H), 7.32-7.28 (m, 2H), 6.68-6.60 (m, 2H), 6.31 (s, NH_2, 2H), 3.93 (d, J = 2.8Hz, 1H), 3.41-3.37 (m, 2H);

4.1.2.14. 1-(2-Aminophenyl)-3-hydroxy-3-(pyridin-4-yl)propan-1-one (4o):
Yield: 82%;MR: 132.136 °C; IR (KBr, cm^{-1}): 3492 (OH), 3426 (NH_2), 1624 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 2H), 7.62 (d, J = 8.0Hz, 1H), 7.36 (s, 2H), 7.30-7.26 (s, 1H), 6.67-6.60 (m, 2H), 6.21 (s NH_2, 2H), 5.30 (d, J = 8.0Hz, 1H), 4.08 (s OH, 1H), 3.38-3.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.20, 152.07, 150.72, 149.90, 135.11, 130.93, 120.73, 117.52, 117.32, 116.02, 68.96, 46.88; LC-MS (ESI): m/z Calcd. for $C_{14}H_{14}N_2O_2$: 242.11, Found 243.18 $[M+H]^+$

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4.1.2.15. 1-(2-Aminophenyl)-3-(furan-3-yl)-3-hydroxypropan-1-one (4p):

Yield: 66%;IR (KBr, cm^{-1}): 3435 (OH), 2920, 1615 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, J = 1.2, 8.0Hz, 1H), 7.46-7.40 (m, 2H), 7.30-7.25 (m, 1H), 6.66-6.62 (m, 2H), 6.45 (s, 1H), 6.30 (s, br, NH_2, 2H), 5.28 (t, J = 6.0Hz, 1H), 3.35 (2d, J = 6.4Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.84, 150.57, 143.25, 138.96, 134.87, 130.99, 120.69, 117.54, 117.43, 115.90, 108.58, 63.46, 46.06; LC-MS (ESI): m/z Calcd. for $C_{13}H_{13}NO_3$: 231.090, Found 255.12 $[M+Na]^+$ (Note: During the nitro reduction of 3-(Furan-3-yl)-3-hydroxy-1-(2-nitrophenyl)propan-1-one (**2p**), along with 1-(2-Aminophenyl)-3-(furan-3-yl)-3-hydroxypropan-1-one(**4p**), furan ring reduced product 1-(2-Aminophenyl)-3-hydroxy-3-(tetrahydrofuran-3-yl)propan-1-one (**4q**) isolated and characterized)

4.1.2.16. 1-(2-Aminophenyl)-3-(furan-2-yl)-3-hydroxypropan-1-one (4q):

Yield: 60%; IR (KBr, cm^{-1}): 3460 (OH), 3006 (NH_2), 1615 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.6Hz, 1H), 7.39 (s, 1H), 7.28 (t, J = 8.0Hz, 1H), 6.64 (t, J = 8.0Hz, 2H), 6.36-6.29 (m, 4H), 3.65-3.64 (m, 1H), 3.53-3.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.37, 155.38, 150.62, 142.02, 134.91, 131.08, 117.61, 117.45, 115.97, 110.25, 106.68, 64.36, 43.67; LC-MS (ESI): m/z Calcd. for $C_{13}H_{13}NO_3$: 231.09, Found NO mass ionization (Note: During the nitro reduction of 3-(Furan-2-yl)-3-hydroxy-1-(2-nitrophenyl)propan-1-one (**2r**), along with 1-(2-Aminophenyl)-3-(furan-2-yl)-3-hydroxypropan-1-one (**4r**), furan ring reduced product 1-(2-Aminophenyl)-3-hydroxy-3-(tetrahydrofuran-2-yl)propan-1-one (**4s**) isolated and characterized)

4.1.2.17. 1-(2-Aminophenyl)-3-hydroxy-3-(thiophen-3-yl)propan-1-one (4r):

Yield: 87%; IR (KBr, cm^{-1}): 3491 (OH), 2903, 1711 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.0Hz, 1H), 7.34-7.21 (m, 3H), 7.06 (d, J = 5.2Hz, 1H), 6.65-6.59 (m, 2H), 6.29 (s, NH_2, 2H), 5.38 (dd, J = 3.2, 7.6Hz, 1H), 3.77 (s, 1H), 3.37 (d, J = 4.0Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.85, 150.60, 144.45, 134.85, 131.05, 126.06, 125.63, 123.27, 120.74, 117.44, 115.91, 66.86, 46.69; LC-MS (ESI): m/z Calcd. for $C_{13}H_{13}NO_2S$: 247.07, Found 248.11 $[M+H]^+$

4.1.2.18. 1-(2-Aminophenyl)-3-hydroxy-3-(thiophen-2-yl)propan-1-one (4s):

Yield: 82%; IR (KBr, cm^{-1}): 3466 (OH), 3423 (NH_2), 1615 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (dd, J = 1.2, 7.6Hz, 1H), 7.30-7.23 (m, 2H), 7.02-6.89 (m, 2H), 6.66-6.63 (m, 2H), 6.32-6.28 (s, NH_2, 2H), 5.55 (dd, J = 4.4, 7.6Hz, 1H), 3.97 (s, OH, 1H), 3.47-3.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.42, 150.61, 146.79, 134.96, 131.96, 126.63, 124.59, 119.93, 117.73, 115.94, 114.85, 66.68, 47.28; LC-MS (ESI): m/z Calcd. for $C_{13}H_{13}NO_2S$: 247.07, Found 248.06 $[M+H]^+$

4.1.2.19. 1-(2-Aminophenyl)-3-hydroxy-3-(tetrahydrofuran-3-yl)propan-1-one (4t):

Yield: 32%;IR (KBr, cm^{-1}): 3446 (OH), 3223 (NH_2), 1615 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.60 (m, 1H), 7.31-7.26 (m, 1H), 6.67-6.63 (m, 2H), 6.29 (s, br, NH_2, 2H), 4.11-3.73 (m, 4H), 3.72-3.56 (m, 1H), 3.26-2.95 (m, 2H), 2.45-2.34 (m, 1H), 2.10-1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.58, 134.91, 131.00, 118.52, 117.50, 115.94, 70.87 & 70.65, 69.85 & 69.45, 68.40 & 68.20, 44.64, 43.87, 29.00 & 28.40; LC-MS (ESI): m/z Calcd. for $C_{13}H_{17}NO_3$: 235.12, Found 236.16 $[M+H]^+$

4.1.2.20. 1-(2-Aminophenyl)-3-hydroxy-3-(tetrahydrofuran-2-yl)propan-1-one (4u):

Yield: 35%;IR (KBr, cm^{-1}): 3436 (OH), 3365 (NH_2), 1616 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75-7.72 (m, 1H), 7.26 (t, J = 8.0Hz, 1H), 6.65-6.62 (m, 2H), 6.26 (s, br, NH_2, 2H), 4.19-4.08 (m, 1H), 3.93-3.74 (m, 4H), 3.37-3.32 (m, 1H), 3.26-3.19 (m, 1H), 3.10-3.01 (m, 2H), 1.46-1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.66 &201.56, 150.50, 134.70 & 134.59, 131.35 & 131.29, 117.36, 115.91, 115.85, 81.42 & 81.17, 70.32 & 70.05, 68.56 & 68.51, 42.71 & 42.21, 29.57 & 27.53, 26.00 & 25.76; LC-MS (ESI): m/z Calcd. for $C_{13}H_{17}NO_3$: 235.12, Found 236.00 $[M+H]^+$

4.1.2.21. 1-(2-Amino-5-methoxyphenyl)-3-hydroxyheptan-1-one (4v):

Yield: 85%;IR (KBr, cm^{-1}): 3433 (OH), 3368 (NH_2), 1610 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.0Hz, 1H), 6.43 (s, br, NH_2, 2H), 6.22 (d, J = 2.4, 8..8Hz, 1H), 6.06 (d, J = 2.4Hz, 1H), 4.17-4.13 (m, 1H), 3.80 (s, 3H), 3.57 (s, OH, 1H), 3.09 (dd, J = 2.4, 17.2Hz, 1H), 2.92-2.86 (m, 1H), 1.64-1.24 (m, 6H), 0.92 (t, J = 10.0Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.19, 164.57, 153.03, 133.20, 112.45, 104.81, 99.15, 68.15, 55.23, 44.80, 36.25, 27.77, 22.70, 14.06; LC-MS (ESI): m/z Calcd. for $C_{14}H_{21}NO_3$: 251.15, Found 252.14 $[M+H]^+$

4.1.2.22. 1-(2-Amino-4-fluorophenyl)-3-hydroxyheptan-1-one (4w):

Yield: 81%;IR (KBr, cm^{-1}): 3438 (OH), 3340 (NH_2), 1634 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, J = 6.3, 8.7Hz, 1H), 6.40 (s, br, NH_2, 2H), 6.38-6.28 (m, 2H), 4.17-4.13 (s, br, 1H), 3.31 (s, OH, 1H), 3.09 (dd, J = 2.7, 17.1Hz, 1H), 2.98-2.89 (m, 1H), 1.65-1.25 (m, 6H), 0.92 (t, J = 6.6Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.71, 166.65 (d), 152.77 (d), 133.98 (d), 115.02, 104.20 (d), 102.46 (d), 67.90, 45.33, 36.19, 27.74, 22.66, 14.00; LC-MS (ESI): m/z Calcd. for $C_{13}H_{18}FNO_2$: 239.13, Found 240.08 $[M+H]^+$

4.1.3. General procedure for the preparation of compounds 5a-w

To a solution of compound **4** (1.0 eq) in toluene (10 vol) was added TsOH (0.5 eq) under argon atmosphere. The reaction mixture was stirred at 120 °C for 1-2 h and then cooled to RT, toluene was removed under reduced pressure, diluted with DCM (30 vol) washed with the saturated $NaHCO_3$ solution (20 vol) followed by saturated brine solution (20 vol). The organic phase dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography to give compound **5a-w** (70-98 %). (**Note:** $ZnCl_2$ (0.75 eq) was used for preparation of pyridine derivatives (**5k-m**))

4.1.3.1. 2-Propyl-2,3-dihydroquinolin-4(1*H*)-one (5a):

MR: 101-104 °C;IR (KBr, cm^{-1}): 3437 (NH), 1653 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (dd, J = 1.6, 8.4Hz, 1H), 7.31-7.26 (m, 1H), 6.72 (t, J = 8.0Hz, 1H), 6.65 (d, J = 8.4Hz, 1H), 4.29 (m, br, NH, 1H), 3.67-3.60 (m, 1H), 2.69-2.65 (m, 1H), 2.51-2.44 (m, 1H), 1.67-1.54 (m, 2H), 1.44-1.33 (m, 2H), 0.97 (t, J = 7.2Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.06, 151.41, 135.14, 127.49, 119.13, 117.92, 115.71, 53.07, 43.94, 37.32, 18.54, 13.95; LC-MS (ESI): m/z Calcd. for $C_{12}H_{15}NO$: 189.12, Found 190.18 $[M+H]^+$

4.1.3.2. 2-Cyclopropyl-2,3-dihydroquinolin-4(1*H*)-one (5b):

MR: 122-125 °C; IR (KBr, cm^{-1}): 3325 (NH), 1656 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (dd, J = 1.6, 8.0Hz, 1H), 7.30-7.27 (m, 1H), 6.72-

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6.65 (m, 2H), 4.48 (s, br, NH, 1H), 2.78-2.60 (m, 3H), 1.09-1.03 (m, 1H), 0.62-0.56 (m, 2H), 0.30-0.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.03, 151.44, 135.19, 127.53, 119.15, 117.95, 115.68, 59.32, 44.26, 15.96, 3.18, 3.12; LC-MS (ESI): m/z Calcd. for $C_{12}H_{13}NO$: 187.10, Found 188.16 $[M+H]^+$

4.1.3.3. 2-Ethyl-2,3-dihydroquinolin-4(1*H*)-one (5c):
IR (KBr, cm^{-1}): 3445 (NH), 1651 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 1.6, 8.0Hz, 1H), 7.30-7.26 (m, 1H), 6.72 (t, *J* = 7.6Hz, 1H), 6.66 (d, *J* = 8.4Hz, 1H), 4.32 (s, br, NH, 1H), 3.58-3.53 (m, 1H), 2.67 (dd, *J* = 3.6, 16.0Hz, 1H), 2.51-2.43 (m, 1H), 1.70-1.63 (m, 2H), 1.01 (t, *J* = 7.8Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.05, 151.44, 135.13, 127.47, 119.12, 117.91, 115.71, 54.66, 43.48, 28.05, 9.63; LC-MS (ESI): m/z Calcd. for $C_{11}H_{13}NO$: 175.10, Found 176.13 $[M+H]^+$

4.1.3.4. 2-Cyclohexyl-2,3-dihydroquinolin-4(1*H*)-one (5d):
MR: 121-125 °C; IR (KBr, cm^{-1}): 3444 (NH), 1650 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (dd, *J* = 1.2, 8.0Hz, 1H), 7.28 (t, *J* = 8.4Hz, 1H), 6.71 (t, *J* = 6.8Hz, 1H), 6.66 (d, *J* = 8.0Hz, 1H), 4.34 (s, NH, 1H), 3.44-3.39 (m, 1H), 2.66-2.51 (m, 2H), 1.83-1.69 (m, 5H), 1.57-1.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.53, 151.62, 135.13, 127.38, 119.01, 117.73, 115.74, 58.12, 41.53, 40.98, 28.87, 28.56, 26.29, 26.07; LC-MS (ESI): m/z Calcd. for $C_{15}H_{19}NO$: 229.14, Found 230.67 $[M+H]^+$

4.1.3.5. 2-Phenyl-2,3-dihydroquinolin-4(1*H*)-one (5e):
MR: 133-136 °C;IR (KBr, cm^{-1}): 3436 (NH), 1650 (OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 1.2, 8.4Hz, 1H), 7.46 (dd, *J* = 1.6, 8.0Hz, 2H), 7.42-7.32 (m, 4H), 6.79 (t, *J* = 8.0Hz, 1H), 6.71 (d, *J* = 8.0Hz, 1H), 4.75 (dd, *J* = 4.0, 13.6Hz, 1H), 4.50 (m, br, NH, 1H), 2.89-2.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.24, 151.53, 141.00, 135.38, 128.99, 128.47, 127.62, 126.61, 119.05, 118.45, 115.88, 58.50, 46.44; LC-MS (ESI): m/z Calcd. for $C_{15}H_{13}NO$: 223.10, Found: 224.62 $[M+H]^+$

4.1.3.6. 2-(4-Bromophenyl)-2,3-dihydroquinolin-4(1*H*)-one (5f):
MR: 165-169 °C;IR (KBr, cm^{-1}): 3467 (NH), 1644 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.0Hz, 1H), 7.52 (d, *J* = 8.4Hz, 2H), 7.40-7.33 (m, 3H), 6.81 (t, *J* = 8.0Hz, 1H), 6.72 (d, *J* = 7.6Hz, 1H), 4.72 (dd, *J* = 4.0, 12.8Hz, 1H), 4.47 (s, NH, 1H), 2.84-2.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.77, 151.28, 140.05, 135.49, 132.13, 128.30, 127.62, 122.25, 119.07, 118.74, 115.94, 57.96, 46.36; LC-MS (ESI): m/z Calcd. for $C_{15}H_{12}BrNO$: 302.01, Found 304.12 $[M+2]^{+2}$ (Note: During the reduction of 3-(4-Bromophenyl)-3-hydroxy-1-(2-nitrophenyl)propan-1-one (**2f**) using Iron (1.0 eq) and acetic acid (3.0) in toluene at reflux for 6 h, directly isolated cyclized 2-(4-Bromophenyl)-2,3-dihydroquinolin-4(1H)-one (**5f)** in 56% yield).

4.1.3.7. 2-(4-(Trifluoromethyl)phenyl)-2,3-dihydroquinolin-4(1*H*)-one (5g):
IR (KBr, cm^{-1}): 3337 (NH), 1610 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.1Hz, 1H), 7.68-7.51 (m, 4H), 7.37 (t, *J* = 6.9Hz, 1H), 6.83 (t, *J* = 7.5Hz, 1H), 6.74 (d, *J* = 8.1Hz, 1H), 4.84 (dd, *J* = 5.1, 12.6Hz, 1H), 4.49 (s, NH, 1H), 2.87-2.76 (m, 2H); LC-MS (ESI): m/z Calcd. for $C_{16}H_{12}F_3NO$: 291.09, Found 292.08 $[M+H]^+$

4.1.3.8. 2-(2,4-Difluorophenyl)-2,3-dihydroquinolin-4(1*H*)-one (5h):
IR (KBr, cm^{-1}): 3287 (NH), 1647 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 8.4, 1.2Hz, 1H), 7.57-7.50 (m, 1H), 7.35 (t, *J* = 8.4Hz, 1H), 6.95-6.79 (m, 3H), 6.72 (d, *J* = 8.4Hz, 1H), 5.09 (t, *J* = 8.4Hz, 1H), 2.87 (d, *J* = 8.1Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.49, 151.17, 135.45, 134.44, 128.54, 127.62, 119.16, 118.80, 117.30, 115.96, 111.89 (d), 111.68, 104.30 (t), 50.64, 44.34; LC-MS (ESI): m/z Calcd. for $C_{15}H_{11}F_2NO$: 259.08, Found 260.54 $[M+H]^+$

4.1.3.9. 2-(4-Methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (5i):
IR (KBr, cm^{-1}): 3436 (NH), 1660 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 10.4Hz, 1H), 7.40-7.30 (m, 3H), 6.93 (d, *J* = 11.6Hz, 2H), 6.78 (t, *J* = 10.0Hz, 1H), 6.69 (d, *J* = 11.2Hz, 1H), 4.70 (dd, *J* = 4.8, 18.0Hz, 1H), 4.43 (s, NH, 1H), 3.83 (s, 3H), 2.93-2.76 (m, 2H); LC-MS (ESI): m/z Calcd. for $C_{16}H_{15}NO_2$: 253.11, Found 254.31 $[M+H]^+$

4.1.3.10. 2-(3-Methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (5j):
MR: 109-112 °C; IR (KBr, cm^{-1}): 3467 (NH), 1655 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 1.6, 10.8Hz, 1H), 7.36-7.25 (m, 2H), 7.04-7.01 (m, 2H), 6.88 (dd, *J* = 2.0, 9.6Hz, 1H), 6.79 (t, *J* = 9.2Hz, 1H), 6.71 (t, *J* = 11.2Hz, 1H), 4.72 (dd, *J* = 6.0, 17.6Hz, 1H), 4.51 (s, NH, 1H), 3.82 (s, 3H), 2.92-2.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.20, 160.01, 151.47, 142.65, 135.38, 130.06, 127.61, 119.02, 118.82, 118.46, 115.89, 113.71, 112.23, 58.46, 55.29, 46.44; LC-MS (ESI): m/z Calcd. for $C_{16}H_{15}NO_2$: 253.11, Found 254.22 $[M+H]^+$

4.1.3.11. 2-(2-Methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (5k):
IR (KBr, cm^{-1}): 3436 (NH), 1660 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 1.6, 8.0Hz, 1H), 7.48 (dd, *J* = 1.2, 7.6Hz, 1H), 7.33-7.25 (m, 2H), 6.98 (t, *J* = 8.0Hz, 1H), 6.90 (d, *J* = 8.0Hz, 1H), 6.76-6.69 (m, 2H), 5.16 (dd, *J* = 4.4, 7.6Hz, 1H), 3.84 (s, 3H), 2.93-2.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.88, 156.57, 151.93, 135.18, 131.91, 129.01, 127.46, 126.41, 120.83, 118.96, 118.02, 116.05, 110.52, 55.32, 51.24, 43.67; LC-MS (ESI): m/z Calcd. for $C_{16}H_{15}NO_2$: 253.11, Found 254.28 $[M+H]^+$

4.1.3.12. 2-(3,4-Dimethylphenyl)-2,3-dihydroquinolin-4(1*H*)-one (5l):
IR (KBr, cm^{-1}): 3327 (NH), 1663 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.0Hz, 1H), 7.32 (t, *J* = 8.8Hz, 1H), 7.22 (s, 1H), 7.17-7.14 (m, 2H), 6.77 (t, *J* = 7.6Hz, 1H), 6.69 (d, *J* = 8.4Hz, 1H), 4.68 (dd, *J* = 3.6, 13.6Hz, 1H), 4.45 (s, br, NH, 1H), 2.92-2.71 (m, 2H), 2.28 (d, *J* = 4.4Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.50, 151.60, 138.46, 137.27, 136.91, 135.31, 130.12, 127.83, 127.61, 123.98, 119.00, 118.32, 115.85, 58.23, 46.248, 19.83, 19.46; LC-MS (ESI): m/z Calcd. for $C_{17}H_{17}NO$: 251.13, Found 252.30 $[M+H]^+$

4.1.3.13. 2-(Pyridin-2-yl)-2,3-dihydroquinolin-4(1*H*)-one (5m):
IR (KBr, cm^{-1}): 3435 (NH), 1611 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 4.8Hz, 1H), 7.84 (dd, *J* = 1.6, 8.0Hz, 1H), 7.73-7.69 (m, 1H), 7.36-7.30 (m, 2H), 7.24-7.18 (m, 1H), 6.78-6.73 (m, 2H), 5.37-5.34 (s, NH, 1H), 4.86 (dd, *J* = 4.4, 12.4Hz, 1H), 3.04-2.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.06, 158.80, 151.06, 149.44, 137.19, 135.46, 131.34, 127.47, 122.99, 120.44, 118.17, 116.14, 57.35, 43.46; LC-MS (ESI): m/z Calcd. for $C_{14}H_{12}N_2O$: 224.09, Found 225.11 $[M+H]^+$

4.1.3.14. 2-(Pyridin-3-yl)-2,3-dihydroquinolin-4(1*H*)-one (5n):
MR: 152-155 °C; IR (KBr, cm^{-1}): 3344 (NH), 1607 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.60 (d, *J* = 3.6Hz, 1H), 7.88 (d, *J* = 8.0Hz, 1H), 7.82 (d, *J* = 7.6Hz, 1H), 7.38-7.32 (m, 2H), 6.82 (t, *J* = 7.6Hz, 1H), 6.74 (d, *J* = 8.0Hz, 1H), 4.80 (dd, *J* = 3.2, 12.8Hz, 1H), 4.57 (s NH, 1H), 2.92-2.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.30, 151.19, 150.00, 148.52, 136.52, 135.54, 134.21, 127.64, 123.80, 119.19, 118.95, 116.01, 56.17, 46.02; LC-MS (ESI): m/z Calcd. for $C_{14}H_{12}N_2O$: 224.09, Found 225.27 $[M+H]^+$

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4.1.3.15. 2-(Pyridin-4-yl)-2,3-dihydroquinolin-4(1*H*)-one (5o):
MR: 174-178 °C; IR (KBr, cm^{-1}): 3435 (NH), 1670 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 5.6Hz, 2H), 7.87 (d, *J* = 8.0Hz, 1H), 7.39-7.35 (m, 3H), 6.83 (t, *J* = 8.0Hz, 1H), 6.76 (d, *J* = 8.4Hz, 1H), 4.78 (t, *J* = 8.4Hz, 1H), 4.57 (s, 1H), 2.83 (d, *J* = 8.8Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.97, 150.95, 150.55, 149.81, 135.63, 127.62, 121.41, 119.18, 119.02, 115.99, 57.35, 45.69; LC-MS (ESI): m/z Calcd. for $C_{14}H_{12}N_2O$: 224.09, Found 224.96 $[M+H]^+$

4.1.3.16. 2-(Furan-3-yl)-2,3-dihydroquinolin-4(1*H*)-one (5p):
IR (KBr, cm^{-1}): 3365 (NH), 1645 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 1.6, 8.0Hz, 1H), 7.47-7.42 (m, 2H), 7.32 (t, *J* = 8.4Hz, 1H), 6.78 (t, *J* = 8.0Hz, 1H), 6.69 (d, *J* = 8.4Hz, 1H), 6.46 (s, 1H), 4.75-4.71 (m, 1H), 4.45 (s, NH, 1H), 2.86-2.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.04, 151.13, 143.79, 139.55, 135.34, 127.59, 125.96, 119.23, 118.54, 115.85, 108.60, 49.72, 45.26; LC-MS (ESI): m/z Calcd. for $C_{13}H_{11}NO_2$: 213.079, Found 214.05 $[M+H]^+$

4.1.3.17. 2-(Furan-2-yl)-2,3-dihydroquinolin-4(1*H*)-one (5q):
MR: 78-82 °C; IR (KBr, cm^{-1}): 3393 (NH), 1663 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 8.0Hz, 1H), 7.39 (s, 1H), 7.32 (t, *J* = 8.4Hz, 1H), 6.78 (t, *J* = 8.0Hz, 1H), 6.70 (d, *J* = 8.0Hz, 1H), 6.34-6.33 (m, 1H), 6.26 (d, *J* = 3.2Hz, 1H), 4.85-4.81 (m, 1H), 4.69 (s, NH, 1H), 3.04-2.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.56, 153.30, 150.41, 142.48, 135.42, 127.47, 119.24, 118.62, 115.98, 110.36, 106.84, 50.80, 49.93; LC-MS (ESI): m/z Calcd. for $C_{13}H_{11}NO_2$: 213.07, Found 214.22 $[M+H]^+$

4.1.3.18. 2-(Thiophen-3-yl)-2,3-dihydroquinolin-4(1*H*)-one (5r):
MR: 131-133 °C; IR (KBr, cm^{-1}): 3336 (NH), 1658 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.0Hz, 1H), 7.36-7.25 (m, 3H), 7.15 (d, *J* = 4.8Hz, 1H), 6.78 (t, *J* = 7.6Hz, 1H), 6.70 (d, *J* = 8.4Hz, 1H), 4.87 (dd, *J* = 4.8, 11.6Hz, 1H), 4.55 (s, NH, 1H), 2.92-2.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.07, 151.19, 142.25, 135.36, 127.60, 126.89, 125.76, 121.91, 119.20, 118.51, 115.83, 53.79, 45.80; LC-MS (ESI): m/z Calcd. for $C_{13}H_{11}NOS$: 229.06, Found 229.88 $[M+H]^+$

4.1.3.19. 2-(Thiophen-2-yl)-2,3-dihydroquinolin-4(1*H*)-one (5s):
MR: 142-145 °C; IR (KBr, cm^{-1}): 3331 (NH), 1665 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 10.4Hz, 1H), 7.34 (t, *J* = 9.6Hz, 1H), 7.29-7.25 (m, 1H), 7.06 (s, 1H), 7.00-6.97 (m, 1H), 6.80 (t, *J* = 10.4Hz, 1H), 6.71 (d, *J* = 10.8Hz, 1H), 5.05 (dd, *J* = 5.7, 8.4Hz, 1H), 4.64 (s, NH, 1H), 3.01-2.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.58, 150.75, 144.48, 135.44, 127.56, 126.87, 125.12, 124.98, 119.28, 118.81, 115.95, 53.73, 47.02; LC-MS (ESI): m/z Calcd. for $C_{13}H_{11}NOS$: 229.06, Found 230.03 $[M+H]^+$

4.1.3.20. 2-(Tetrahydrofuran-3-yl)-2,3-dihydroquinolin-4(1*H*)-one (5t):
MR:114-117 °C; IR (KBr, cm^{-1}): 3466 (NH), 1665 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.0Hz, 1H), 7.30 (t, *J* = 8.0Hz, 1H), 6.76-6.65 (m, 2H), 4.01-3.56 (m, 5H), 2.59-2.46 (m, 2H), 2.10-2.06 (m, 1H), 2.03-1.65 (m, 2H); ^{13}C NMR ($CDCl_3$-d_3, 100 MHz): δ 193.32 & 193.26, 150.86 & 150.34, 135.34 & 135.28, 127.48 & 127.42, 119.20 & 119.00, 118.23 & 118.12, 115.88 & 115.78, 70.81 & 70.12, 68.26 & 68.14, 56.53 & 56.12, 43.16 & 42.95, 42.66 & 42.61, 29.65 & 29.31; LC-MS (ESI): m/z Calcd. for $C_{13}H_{15}NO_2$: 217.110, Found 218.08 $[M+H]^+$

4.1.3.21. 2-(Tetrahydrofuran-2-yl)-2,3-dihydroquinolin-4(1*H*)-one (5u):
IR (KBr, cm^{-1}): 3435 (NH), 1662 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.79 (m, 1H), 7.33-7.27 (m, 1H), 6.74-6.67 (m, 2H), 3.98-3.56 (m, 4H), 2.55-2.17 (m, 2H), 2.08-1.65 (m, 4H); LC-MS (ESI): m/z Calcd. for $C_{13}H_{15}NO_2$: 217.110, Found 218.13 $[M+H]^+$

4.1.3.22. 2-Butyl-6-methoxy-2,3-dihydroquinolin-4(1*H*)-one (5v):
IR (KBr, cm^{-1}): 3317 (NH), 1636 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.4Hz, 1H), 6.32 (dd, *J* = 2.0, 8.4Hz, 1H), 6.08 (d, *J* = 2.0Hz, 1H), 3.77 (s, 3H), 3.64-3.57 (m, 1H), 2.62 (dd, *J* = 4.0, 8.0Hz, 1H), 2.47-2.39 (m, 1H), 1.66-1.25 (m, 6H), 0.97-0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.71, 165.42, 153.34, 129.70, 113.56, 106.65, 98.12, 55.30, 53.44, 43.67, 34.95, 27.49, 22.59, 13.93; LC-MS (ESI): m/z Calcd. for $C_{14}H_{19}NO_2$: 233.14, Found 234.17 $[M+H]^+$

4.1.3.23. 2-Butyl-7-fluoro-2,3-dihydroquinolin-4(1*H*)-one (5w):
MR: 90-93 °C; IR (KBr, cm^{-1}): 3347 (NH), 1645 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (t, *J* = 8.7Hz, 1H), 6.46-6.39 (m, 1H), 6.30 (d, *J* = 10.2Hz, 1H), 4.42 (s, br, NH, 1H), 3.67-3.58 (m, 1H), 2.70-2.63 (m, 1H), 2.51-2.41 (m, 1H), 1.64-1.58 (m, 2H), 1.38-1.30 (m, 4H), 0.95-0.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.63, 167.42 (d), 153.08 (d), 130.51 (d), 115.95, 106.26 (d), 101.26 (d), 53.30, 43.53, 34.74, 27.42, 22.54, 13.92; LC-MS (ESI): m/z Calcd. for $C_{13}H_{16}FNO$: 221.12, Found 222.12 $[M+H]^+$

4.2. Biology (Alpha glucosidase enzyme inhibition assay):

4.2.1. Test concentration:
The stock solutions (10mM) of standards and each test substances were prepared in 100% Dimethyl Sulfoxide (DMSO, Sigma Chemical Co., St. Louis, MO) and further diluted with PBS to obtain an experimental concentration of 1-0.25 mM (also 0.125 and 0.062 for potent compounds).

4.2.2. Protocol for α-glucosidase enzyme assay:
The inhibitory activity assay procedure was performed by optimizing the previously reported method (Damsud et al., 2013).[14] α-glucosidase enzyme (0.1U/ml) was dissolved in the 1mM concentration of phosphate buffer (pH 6.9) and was prepared fresh every time. The initial step was performed by mixing 10 µL of the test sample with 40 µL of prepared enzyme solution and incubated for 15-20 min at 37 °C. Then 40 µL of p-nitrophenyl-α-D-glycopyranoside (PNPG) substrate (0.1mM) was added and incubated for 45-60 min. The release of p-nitrophenol by quenching effect was determined with the addition of 100 µL of 0.1 M Na_2CO_3. Further, the enzymatic activity was quantified in proportion to the level of p-nitrophenol spectrophotometrically with absorbance reading at 415nm. Blank reading was taken without the test compound and with enzyme and substrate. Acarbose, Voglibose and Miglitol were used as positive controls.

4.2.3. Data interpretation:

The readings taken at 415nm were further evaluated for their percentage inhibition of test compounds (Table 3). The equation used was:

((Ablank – Asample) / Ablank) *100

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The IC_{50} values were calculated plotting graphs with percentage inhibition on the y-axis and log concentrations on x-axis using graph pad prism v 6.0. The IC_{50} values are reported as best fit value after normalization of data (n=3)

Conclusions

In conclusion, we have developed an efficient methodology by employing acid catalysts for the synthesis of aza-flavanones, evaluated their α-glucosidase inhibition activity as well as molecular docking study. Aza-flavanone derivatives **5a, 5g, 5h, 5r, and 5w** were identified as potent α-glucosidase inhibitors compared to reference standards. Particularly compound **5g** displayed **6-8** fold higher activity compared to reference standards. This indicates that this particular library may be a valuable addition to understanding numerous cellular processes involving α-glucosidase inhibition. Based on the present results, these derivatives can be taken forward to assist the accelerated drug discovery of anti-diabetics.

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Conflict of Interest

The authors declare no competing interest.

Notes and references

1. (a) A. S. Dabhi, N. R. Bhatt, M. J. Shah, *J. Clin. Diagn. Res.,* 2013, **7**, 3023-3027. (b) H. Delgado, T. Lehmann, E. Bobbioni-Harsch, J. Ybarra, A. Golay, *Diabetes. Metab.,*2002, **28**, 195-200.
2. (a) W. D. Seo, J. H. Kim, J. E. Kang, H. W. Ryu, M. J. Curtis-Long, H. S. Lee, M. S. Yang, K. H. Park, *Bio. Med. Chem. Lett.,* 2005, **15**, 5514-5516. (b) C. C. Chang, S. L. Ho, S. S. Lee, *Bio. Med. Chem.,* 2015, **23**, 3383-3396.
3. (a) D. Ma, C. Xia, J. Jiang, J. Zhang, W. Tang, *J. Org. Chem.,* 2003, **68**, 442-451. (b) D. Ma, C. Xia, J. Jiang, J. Zhang, *Org. Lett.*, 2001, **3**, 2189-2191.
4. S. Kawaii, K. Endo, T. Tokiwano, Y. Yoshizawa, *Anticancer. Res.,* 2012, **32**, 2819-2826.
5. P. Hradil, J. Hlavac, M. Soural, M. Hajdúch, M. Kolar, R. Vecerova, *Mini-Rev. Med. Chem.,* 2009, **9**, 696-708. (b) S. X. Zhang, J. Feng, S. C. Kuo, A. Brossi, E. Hamel, A. Tropsha, K. H. Lee, *J. Med. Chem.,* 2000, **43**, 167-177. (c) Y. Xia, Z. Y. Yang, P. Xia, K. F. Bastow, Y. Tachibana, S. C. Kuo, E. Hamel, T. Hackl, K. H. Lee, *J. Med. Chem.,* 1998, **41**, 1155-1163.
6. S. Chandrasekhar, S. N. Pushpavalli, S. Chatla, D. Mukhopadhyay, B. Ganganna, K. Vijeender, P. Srihari, C. R. Reddy, M. J. Ramaiah, U. Bhadra, *Bio. Med. Chem. Lett.,* 2012, **22**, 645-648.
7. B. Evans, K. Rittle, M. Bock, R. DiPardo, R. Freidinger, W. Whitter, G. Lundell, D. Veber, P. Anderson, *J. Med. Chem.,* 1988, **31**, 2235-2246.
8. N. Ahmed, J. E. van Lier, *Tett. Lett.,* 2006, **47**, 2725-2729.
9. N. Ahmed, J. E. van Lier, *Tett. Lett.,* 2007, **48**, 13-15.
10. M. Chelghoum, M. Bahnous, A. Bouraiou, S. Bouacida, A. Belfaitah, *Tett. Lett.,* 2012, **53**, 4059-4061.
11. S. Chandrasekhar, K. Vijeender, C. Sridhar, *Tett. Lett.,* 2007, **48**, 4935-4937.
12. R. P. Pandit, K. Sharma, Y. R. Lee, S*ynthesis,* 2015, **47**, 3881-3890.
13. P. R. Chopade, T. A. Davis, E. Prasad, R. A. Flowers, *Org. Lett.,* 2004, **6**, 2685-2688.
14. T. Damsud, S. Adisakwattana, P. Phuwapraisirisan, *Phytochem. Lett.,* 2013, **6**, 350-354.
15. Schrödinger Release 2014-1: Maestro, version 9.7, Schrödinger, LLC, New York, NY, 2014.
16. K. Yamamoto, H. Miyake, M. Kusunoki, S. Osaki, *Febs J.,* 2010, **277**, 4205-4214.