*Journal of Pharmaceutical Research International*

***33(28B): 81-92, 2021; Article no.JPRI.68512***
***ISSN: 2456-9119***
*(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)*

# Synthesis, Drug Likeness and *In-vitro* Screening of Some Novel Quinazolinone Derivatives for Anti-Obesity Activity

**Pratik G. Modh[1*] and Laxman J. Patel[1]**

*[1]Faculty of Pharmacy, Ganpat University, Ganpat Vidyanagar, Mehsana-384012,Gujarat, India.*

***Authors' contributions***

*This work was carried out in collaboration between both authors. Author PGM designed the study, performed the synthesis, characterization and anti-obesity activity, wrote the protocol, and wrote the first draft of the manuscript. Author LJP managed the analyses of the study, the literature searches and results. Both the authors read and approved the final manuscript.*

***Article Information***

DOI: 10.9734/JPRI/2021/v33i28B31541
Editor(s):
(1) Syed A. A. Rizvi, Nova Southeastern University, USA.
Reviewers:
(1) Trimurti L. Lambat, Manoharbhai Patel College of Arts, Commerce & Science, India.
(2) Rajan Kumar, Lovely Professional University, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/68512

***Original Research Article***

***Received 02 March 2021***
***Accepted 09 May 2021***
***Published 11 May 2021***

## ABSTRACT

**Aim:** A series of novel quinazolinone derivates was synthesized and assessed for their ability to inhibitory action on pancreatic lipase. The cyclization of quinazolinone-4(3H)-one derivatives was achieved, whereas carbon-carbon cross coupling reactions were carried out on cyclized quinazolinone-4(3H)-one. This synthesis method afforded corresponding 2, 3 and 6 substituted quinazolin-4(3H)-ones **(3a to 3m)** with moderate to high yields.
**Methods:** Benzamide derivatives **(1a-1b)** were synthesized from anthranilic acid using acid-amine reaction, followed by cyclization using catalytic p-toluene sulfonic acid and oxidation using (diacetoxyiodo)benzene to give bromo substituted quinazolin-4(3H)-ones **(2a-2b)**, which were cross coupled to suitable boronic acid using Suzuki-Miyaura condition to obtain desired compound **(3a-3m)**. All synthesized compounds were characterized by FTIR, proton NMR, LC-MS analysis, checked for their drug likeness, absorption and evaluated for *in vitro* pancreatic lipase inhibition activity.
**Results:** Analytical interpretation of all compounds with infrared, proton NMR and LC-MS spectroscopy confirmed their correct structure. All compounds **(3a-3m)** show good absorption and

**Corresponding author: E-mail: modh044@gmail.com;*

have reasonably good molecular properties except **3c** and 3m which violate two criteria for Lipinski's rule. Whereas, Compounds **3l** and **3m** showed $IC_{50}$ value of 13.13±0.84 µg/mL and 13.80±1.27 µg/mL respectively comparable to the Orlistat (12.72±0.97µg/mL), a US FDA approved drug for the treatment of obesity.

**Conclusion:** Pancreatic lipase is an important lipolytic enzyme, synthesized and secreted through pancreas, plays an important role in dietary trigycerol absorption and metabolism. Therefore, reducing fat absorption through pancreatic lipase inhibition is a promising strategy to treat obesity. Based upon our findings, compounds **3l** and **3m** can be further developed as potent anti-obesity agents.

*Keywords: Quinazolin-4(3H)-one; carbon-carbon cross coupling reactions; cyclization; pancreatic lipase inhibition; anti-obesity agents.*

## ABBREVIATIONS

*TLC : Thin layer chromatography;*
*FTIR : Fourier transform infrared;*
*NMR : nuclear magnetic resonance;*
*LC-MS : Liquid chromatography–mass spectrometry;*
*$IC_{50}$ : The half maximal inhibitory concentration.*

## 1. INTRODUCTION

The quinazolinones have been reported to possess a vast range of biological activities [1] including effects on the cardiovascular system such as antihypertensive, antiarrhythmic, vasodilatory, and lipid-lowering effects. Additionally, quinazolinones exhibit anti-inflammatory activity by inhibiting cyclooxygenase activity and leukocyte function. The Quinazolinones can also inhibit monoamine oxidase, aldose reductase, tumor necrosis factor R, thymidylate synthase, pyruvic acid oxidation, and acetylcholine-esterase activity and therefore used as antitumor, antiulcer, antiplatelet aggregation (glycoprotein IIb/ IIIa inhibitors) and hypoglycemic agents [2-7]. Various quinazolin-4(3H)-ones with different substitutions have been reported to have anti-diabetic [8], anti-hyperlipidemic [9], anti-hyperlipidemic and hypoglycemic activity [10]. Additionally, Ghrelin receptor antagonism [2], melanin concentrating hormone receptor 1 (MCHR1) antagonism [11] and α-glucosidase inhibition [12] are amongst their other mechanism for the treatment of diabetes and obesity.

A variety of methods for the synthesis of substituted quinazolin-4(3H)-ones have been reported. The most common method is based on the Niementowski reaction by the fusion of anthranilic acid analogues with amides, proceeding via an o-aminobenzamides intermediate [13], using various catalysts like graphite at 220 $^0$C [14,15], UHP (urea hydrogen peroxide)-potassium carbonate [16], DMSO and ionic liquid as a chemical Catalysts [17-19]. Various 2-substituted quinazolinones can be synthesized from functional iminophosphoranes bearing an amido group using aza-wittig

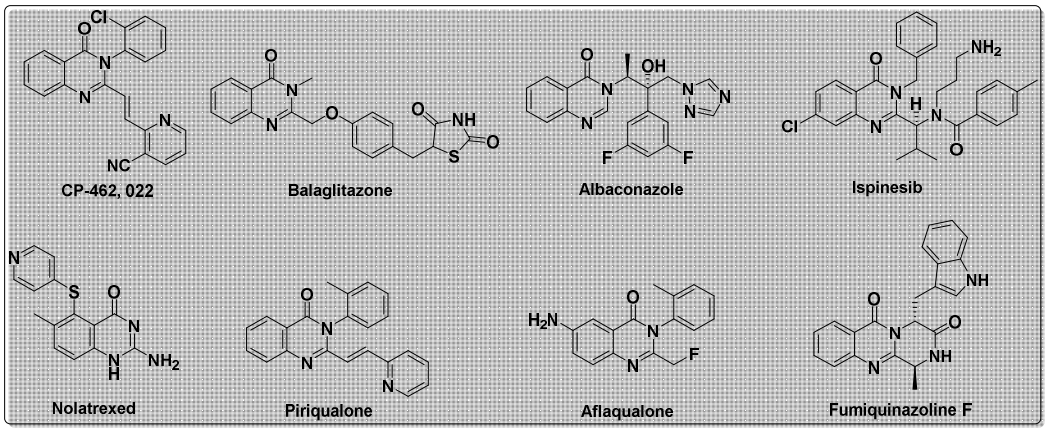


**Fig. 1. Some quinazolinone drugs**

reactions which utilize reagents like triphenyl phosphine [20], benzyl isocyanate, carbon disulfide [21] and polymer PEG 4000 [22]. Quinazolinone-4(3H) ones have also been synthesized from benzoxazinone intermediate like piriqualone using carbodiimide (DCC) [23], N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDCI) [24], ferrous chloride or bromide and sodium acetate in acetic acid [25] and via electrolysis method using $LiClO_4$ and other solvents [26-27]. Some quinazolinone drugs have been shown below in Fig. 1.

In the present work, we synthesized novel quinazolin-4(3H)-one derivatives and evaluated for pancreatic lipase inhibition activity which support their future development as anti-obesity agent.

## 2. MATERIAL AND METHODS

The novel synthesis scheme for the title compounds is outlined in Fig. 2. Melting points of all synthesized compounds were determined in open capillaries using Veego melting point apparatus, Model VMP-D (Veego India ltd., Mumbai, India) and were uncorrected. Infrared spectra were recorded on SHIMADZU-IR Affinity-1S Fourier Transform Infrared (FTIR) spectrophotometer using attenuated total reflection (ATR) technique. LC–MS analysis for all samples were carried out using WATERS ACQUITY UPLC H class spectrometer with PDA and SQ detector. Samples were prepared in 2mM ammonium acetate and injected into the BEH C18 (502.1 mm) 1.7µm column for detection using 0.1% formic acid in water: acetonitrile as mobile phase with. 1H-NMR spectra were recorded on Brucker 400 MHz Avance III HD instrument with 5mm PABBO BB/19F-1H/D Z-GRD Z108618 probe using DMSO D6 as a solvent and data were processed using Topspin 3.2 software. TLC was performed on precoated alumina silica gel 60 F254 (Merck) using different polarity ratios of ethylacetate: n-hexane as mobile phase and detection was done using UV light. The resulting compounds were purified by recrystallization using suitable solvent or by flash column chromatography.

General synthetic procedures used for the preparation of the target compounds are described below.

### 2.1 Synthesis of 2-amino- N-substituted-5-bromobenzamide (1a-1b)

To the mixture of 2-amino-5-bromobenzoic acid (1.0 mmol), cyclohexyl amine or benzyl amine (1.0 mmol) in tetrahydrofuran (15 time), N, N-diisopropylethylamine (2.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 mmol) and 1-hydroxybenzotriazole (0.5 mmol) were added successively and stirred for 12 h at room temperature. The progression of the reaction was

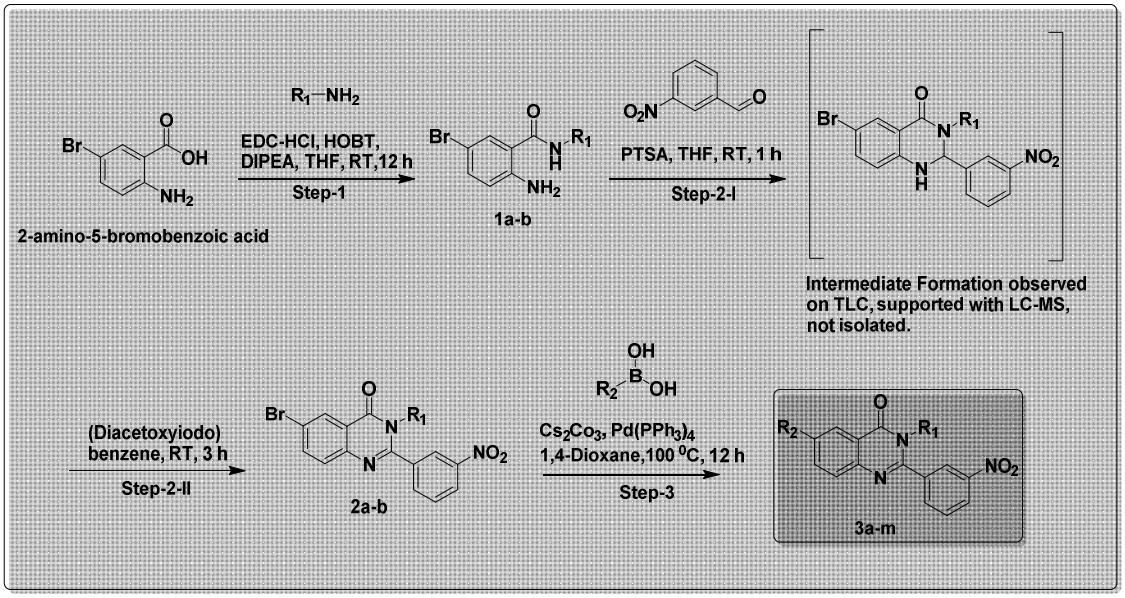


**Fig. 2. Synthetic scheme of 2, 3 and 6-trisubstituted quinazolin-4(3*H*)-one (3a-3m)**

monitored with TLC using ethylacetate: n-hexane (4:1) as mobile phase. The reaction mixture was poured to water, extracted with ethylacetate, washed with brine, dried over sodium sulfate and concentrated under reduced pressure to get the crude product which was purified by trituration using diethyl ether and dried to obtain the desired product as 2-amino-5-bromo-N-cyclohexyl benzamide **(1a)** or 2-amino-N-benzyl-5-bromobenzamide **(1b)**.

## 2.2 Synthesis of 3-substituted-6-bromo-2-(3-nitrophenyl) quinazolin-4(3*H*)-one (2a-2b)

To a solution of 2-amino-5-bromo-N-cyclohexyl benzamide **(1a)** or 2-amino-N-benzyl-5-bromobenzamide **(1b)** (1.0 mmol) and 3-nitrobenzaldehyde (1.2 mmol) in tetrahydrofuran (10 time), p-toluene sulfonicacid monohydrate (0.2 mmol) was added and stirred for 1 h at room temperature. Consumption of 1a or 1b was checked with TLC using ethylacetate: n-hexane (1:1) as mobile phase, followed by addition of (diacetoxyiodo) benzene (1.5 mmol) portion-wise and mixture was stirred for another 3 h at room temperature. After checking the reaction completion with TLC using ethylacetate: n-hexane (1:1) as mobile phase, the reaction mixture was poured to water, extracted with ethylacetate, washed with brine, dried over sodium sulfate and concentrated under reduced pressure to get the crude product which was purified by flash column chromatography using 20-30 % ethylacetate in n-hexane as mobile phase, eluting the desired product as 6-bromo-3-cyclohexyl-2-(3-nitrophenyl)quinazolin-4(3H)-one **(2a)** or 3-benzyl-6-bromo-2-(3-nitrophenyl) quinazolin-4(3H)-one **(2b)**.

## 2.3 Synthesis of 2, 3 and 6 substituted quinazolin-4(3*H*)-one (3a to 3m)

To the mixture of 2a or 2b (1.0 mmol) and Boronic acid derivative (1.5 mmol) in 1, 4-dioxane (20 time) was added cesium carbonate (3.0 mmol) in a glass sealed tube and the reaction mixture was degassed with nitrogen for 15 min, followed by the addition of tetrakis (triphenylphosphine) palladium (0) ($Pd(PPh_3)_4$) (0.05 mmol) and heated to 100 $^0$C for 12 h. The reaction was monitored with TLC using ethylacetate: n-hexane as mobile phase. The reaction mixture was poured to water, extracted with ethylacetate, washed with brine, dried over sodium sulfate, concentrated under reduced pressure to give the crude product which was purified by flash column chromatography using ethylacetate: n-hexane as mobile phase to give the desired product **(3a-3m)** with good yield.

## 2.4 Prediction of Drug Likeness and Absorption

The prediction of molecular properties like drug likeliness and absorption were carried out by Molinspiration Cheminformatics Software available online. All synthesized molecules were sketched in ChemDraw 15 and they were copied as SMILES and saved. The Molinspiration home page was opened online, where a link for "Calculation of Molecular Properties and Bioactivity Score" was opened. All saved SMILES for synthesized compounds were pasted and properties like Log P, molecular weight, number of hydrogen bond acceptors, number of hydrogen bond donors, number of rotatable bonds, molecular volume, total polar surface area were calculated and saved. Absorption (%abs) was calculated by %abs = 109- (0.345 X TPSA) [28].

## 2.5 Pancreatic Lipase Inhibitory Activity (Anti-Obesity Activity)

### 2.5.1 Chemicals & reagents

4-methylumbelliferyl oleate (4-MU oleate), Tris-HCl, Sodium chloride, Calcium chloride, sodium citrate, orlistat.

### 2.5.2 Instrument

Fluorometrical microplate reader.

### 2.5.3 Experimental method

*In vitro* pancreatic lipase inhibition activity was performed as described by Nakai et al. [29]. Pancreatic lipase activity was measured using 4-methylumbelliferyl oleate (4-MU oleate) as a substrate. 25 µl of different concentrations (10, 50, 100 µg/mL) of test compound (3a to 3m) or standard (Orlistat) (Positive control) dissolved in water and 50 µL of 0.1 mM 4-MU dissolved in buffer consisting of 13 mM Tris-HCl, 150 mM NaCl, and 1.3 mM $CaCl_2$ (pH 8.0), were mixed in the microtiter plate well, followed by addition of 25 µL of lipase solution (50 U/mL) prepared in the above buffer to start the enzyme reaction. After incubation at 25 °C for 30 min, 100 µl of 0.1 M sodium citrate (pH 4.2) was added to stop the

reaction. The amount of 4-methylumbelliferone released by lipase was measured using a fluorometrical microplate reader at an excitation wavelength of 355 nm and an emission wavelength of 460 nm. The IC50 value of the test sample (3a to 3m) and standard (orlistat) was obtained from the least-squares regression analysis performed by plotting logarithm of the sample concentration (log) *versus* the pancreatic lipase activity (%).

## 3. RESULTS AND DISCUSSION

In the first step, benzamide derivatives **(1a-1b)** were synthesized from anthranilic acid using acid-amine coupling condition. In the second step, substituted benzamide derivatives were cyclized using catalytic p-toluene sulfonic acid, followed by oxidation using (diacetoxyiodo)benzene to give bromo substituted quinazolin-4(3H)-ones **(2a-2b)**, which were cross coupled to suitable boronic acid using Suzuki-Miyaura condition in third step to obtain desired compound **(3a-3m)**. All synthesized compounds were characterized and confirmed with physical parameters like melting point, IR, LC-MS and 1H-NMR spectroscopy.

### 3.1 Physical and Spectral Data of Synthesized Compounds

#### 3.1.1 2-amino-5-bromo-N-cyclohexylbenzamide (1a)

Off white solid product; MP: 195-199°C; Rf: 0.55 (TLC, Ethylacetate: n-hexane = 4: 1); Yield: 70%.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.12 (d, J=7.8 Hz, 1H), 7.63 (d, J=2.3 Hz, 1H), 7.25 (dd, J=8.7, 2.3 Hz, 1H), 6.65 (d, J=8.8 Hz, 1H), 6.50 (s, 2H), 3.70 (s, 1H), 1.76 (dd, 22.6, 7.7 Hz, 4H), 1.61 (d, J=12.8 Hz, 1H), 1.28 (t, J=9.6 Hz, 4H), 1.12 (d, J=11.7 Hz, 1H). LC-MS m/z = 297/299 $[M]^+$.

#### 3.1.2 2-amino-N-benzyl-5-bromobenzamide (1b)

Off white solid product; MP: 204-208°C; Rf: 0.62 (TLC, Ethylacetate: n-hexane = 4: 1); Yield: 79%.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.93 (t, J=6.0 Hz, 1H), 7.73 (d, J=2.4 Hz, 1H), 7.37-7.20 (m, 6H), 6.68 (d, J=8.7 Hz, 1H), 6.63 (s, 2H), 4.40 (d, J=5.9 Hz, 2H). LC-MS m/z = 305/307 $[M]^+$.

#### 3.1.3 6-bromo-3-cyclohexyl-2-(3-nitrophenyl) quinazolin-4(3*H*)-one (2a)

Cream solid product; MP: 192-196°C; Rf: 0.44 (TLC, Ethylacetate: n-hexane = 1: 1); Yield: 68%.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.54 (s, 1H), 8.43 (d, J=8.4 Hz, 1H), 8.27 (d, J=2.4 Hz, 1H), 8.12 (d, J=7.7 Hz, 1H), 8.01 (dd, J=8.8, 2.5 Hz, 1H), 7.87 (t, J=8.0 Hz, 1H), 7.64 (dd, J=8.6 Hz, 2.3 Hz, 1H), 3.66 (m, 1H), 1.82 (d, J=12.4 Hz, 2H), 1.70 (d, J= 13.2 Hz, 2H), 1.49 (d, J=13.0 Hz, 1H), 1.24 (d, J=13.0 Hz, 1H), 1.09 (d, J=13.3 Hz, 1H), 0.93-0.86 (m, 3H).LC-MS m/z = 428/430 $[M]^+$.

#### 3.1.4 3-benzyl-6-bromo-2-(3-nitrophenyl) quinazolin-4(3*H*)-one (2b)

Cream solid product; MP: 201-205°C; Rf: 0.48 (TLC, Ethylacetate: n-hexane = 1: 1); Yield: 80%.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.39-8.30 (m, 2H), 8.25 (d, J=8.3 Hz, 1H), 8.13-8.03 (m, 1H) 7.87 (t, J=7.8 Hz, 1H), 7.71 (q, J=7.9 Hz, 2H), 7.26-7.16 (m, 3H), 6.94 (dd, J=10.1, 5.0 Hz, 2H), 5.18 (s, 2H). LC-MS m/z = 436/438 $[M]^+$.

#### 3.1.5 3-benzyl-6-cyclopropyl-2-(3-nitrophenyl)quinazolin-4(3*H*)-one (3a)

Off white solid product; MP: 170-174°C; Rf: 0.35 (TLC, Ethylacetate: n-hexane = 1: 4); Yield: 55%.

IR ($u_{max}$, $cm^{-1}$): 3030 (Alkane C-H), 2922, 2854 (Ar. C-H), 1681 (C=O), 1620 (C=N), 1587 (Ar. C=C), 1535 (N-O asymmetrical), 1492, 1342 (N-O symmetrical). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.33 (d, J=8.4 Hz, 1H), 8.24 (s, 1H), 7.94 (s, 1H), 7.86 (d, J=7.6 Hz, 1H), 7.76 (t, J=8.4 Hz, 1H), 7.68 (s, 2H), 7.29-7.20 (m, 3H), 6.90 (d, J=6.8 Hz, 2H), 5.18 (s, 2H), 2.20 (p, J=4.5 Hz, 1H), 1.09 (d, J=6.8 Hz, 2H), 0.83 (d, J=4.4 Hz, 2H). LC-MS m/z = 398.31 $[M+H]^+$.

#### 3.1.6 3-cyclohexyl-6-(3,5-dichlorophenyl)-2-(3-nitrophenyl)quinazolin-4(3*H*)-one (3b)

White solid product; MP: 185-189°C; Rf: 0.38 (TLC, Ethylacetate: n-hexane = 1: 4); Yield: 61%.

IR ($u_{max}$, $cm^{-1}$): 2927, 2852 (Ar. C-H), 1676 (C=O), 1616 (C=N), 1583 (Ar. C=C), 1529 (N-O asymmetrical), 1492, 1348 (N-O symmetrical), 835, 800 (C-Cl). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.56 (s, 1H), 8.45 (s, 1H), 8.43 (s, 1H), 8.24 (d,

J=9.0 Hz, 1H), 8.14 (d, J=8.3 Hz, 1H), 8.03 (d, J=16.7 Hz, 1H), 7.89-7.86 (m, 2H), 7.78 (t, J=8.0 Hz, 1H), 7.68 (s, 1H), 3.71-3.69 (m, 1H), 2.60-2.50 (m, 2H), 1.86 (d, J=12.0 Hz, 2H), 1.73 (d, J=12.7 Hz, 2H), 1.50 (d, J=12.9 Hz, 1H), 1.11 (d, J=13.6 Hz, 1H), 0.93 (d, J=13.2 Hz, 2H). LC-MS m/z = 494.34 $[M]^+$.

#### 3.1.7 3-benzyl-6-(3,5-dichlorophenyl)-2-(3-nitrophenyl)quinazolin-4(3*H*)-one (3c)

White solid product; MP: 201-205°C; Rf: 0.38 (TLC, Ethylacetate: n-hexane = 1: 4); Yield: 35%.

IR ($u_{max}$, $cm^{-1}$): 2926, 2856 (Ar. C-H), 1674 (C=O), 1616 (C=N), 1585 (Ar. C=C), 1529 (N-O asymmetrical), 1492, 1348 (N-O symmetrical), 837, 798 (C-Cl). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.53 (s, 1H), 8.38-8.24 (m, 3H), 7.95-7.81 (m, 4H), 7.77-7.66 (m, 2H), 7.22 (d, J=5.7 Hz, 3H), 6.95 (d, J=6.8 Hz, 2H), 5.22 (s, 2H). LC-MS m/z = 502.29 $[M]^+$.

#### 3.1.8 3-benzyl-2-(3-nitrophenyl)-6-(thiophen-3-yl) quinazolin-4(3*H*)-one (3d)

Light brown solid product; MP: 203-207°C; Rf: 0.44 (TLC, Ethylacetate: n-hexane = 2: 3); Yield: 53%.

IR ($u_{max}$, $cm^{-1}$): 3093 (Alkane C-H), 1676 (C=O), 1618 (C=N), 1581 (Ar. C=C), 1529 (N-O asymmetrical), 1487, 1350 (N-O symmetrical). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.52 (s, 1H), 8.38-8.23 (m, 3H), 8.16 (s, 1H), 7.89 (d, J=7.7 Hz, 1H), 7.83-7.67 (m, 4H), 7.22 (d, J=6.0 Hz, 3H), 6.94 (d, J=6.9 Hz, 2H), 5.21 (s, 2H). LC-MS m/z = 440.14 $[M+H]^+$.

#### 3.1.9 3,6-dibenzyl-2-(3-nitrophenyl) quinazolin-4(3*H*)-one (3e)

Off white solid product; MP: 187-191°C; Rf: 0.48 (TLC, Ethylacetate: n-hexane = 2: 3); Yield: 33%.

IR ($u_{max}$, $cm^{-1}$): 3078, 3030 (Alkane C-H), 2924, 2852 (Ar. C-H), 1676 (C=O), 1616 (C=N), 1591 (Ar. C=C), 1529 (N-O asymmetrical), 1487, 1344 (N-O symmetrical). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.32 (d, J=8.4 Hz, 1H), 8.20 (d, J=4.8 Hz, 1H), 8.09 (d, J=4.9 Hz, 1H), 7.87-7.76 (m, 2H), 7.68 (t, J=7.1 Hz, 2H), 7.37-7.27 (m, 4H), 7.21 (dt, J=10.1, 5.8 Hz, 4H), 6.90 (s, 2H), 5.16 (s, 2H), 4.17 (s, 2H). LC-MS m/z = 448.2 $[M+H]^+$.

#### 3.1.10 3-benzyl-2,6-bis(3-nitrophenyl) quinazolin-4(3H)-one (3f)

Light yellow solid product; MP: 192-196°C; Rf: 0.42 (TLC, Ethylacetate: n-hexane = 2: 3); Yield: 25%.

IR ($u_{max}$, $cm^{-1}$): 3088 (Alkane C-H), 2962, 2922, 2852 (Ar. C-H), 1683 (C=O), 1616 (C=N), 1575 (Ar. C=C), 1525 (N-O asymmetrical), 1500, 1348 (N-O symmetrical). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.60 (d, J=8.6 Hz, 2H), 8.36 (s, 3H), 8.40-8.25 (m, 2H), 7.93-7.80 (m, 3H), 7.73 (t, J=7.9 Hz, 1H), 7.22 (d, J=6.1 Hz, 3H), 6.96 (d, J=6.5 Hz, 2H), 5.22 (s, 2H). LC-MS m/z = 479.39 $[M+H]^+$.

#### 3.1.11 3-benzyl-6-(4-chlorophenyl)-2-(3-nitrophenyl) quinazolin-4(3*H*)-one (3g)

Off white solid product; MP: 203-207°C; Rf: 0.44 (TLC, Ethylacetate: n-hexane = 2: 3); Yield: 60%.

IR ($u_{max}$, $cm^{-1}$): 1683 (C=O), 1616 (C=N), 1558 (Ar. C=C), 1527 (N-O asymmetrical), 1475, 1350 (N-O symmetrical), 821(C-Cl). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.48 (s, 1H), 8.35 (d, J=8.3 Hz, 1H), 8.25 (d, J=8.2 Hz, 2H), 7.87 (dd, J=15.5, 8.2 Hz, 4H), 7.72 (t, J=8.0 Hz, 1H), 7.60 (d, J=8.2 Hz, 2H), 7.22 (d, J=5.9 Hz, 3H), 6.94 (d, J=6.7 Hz, 2H), 5.21 (s, 2H). LC-MS m/z = 391.3 [M-77] +; 468.7 $[M+H]^+$.

#### 3.1.12 4-(3-cyclohexyl-2-(3-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl)benzoicacid (3h)

Light yellow solid product; MP: 182-186°C; Rf: 0.24 (TLC, Ethylacetate: n-hexane = 4: 1); Yield: 43%.

IR ($u_{max}$, $cm^{-1}$): 3068 (Alkane C-H), 2939, 2854 (Ar. C-H), 1697 (C=O), 1670 (C=O), 1608 (C=N), 1585 (Ar. C=C), 1529 (N-O asymmetrical), 1483, 1348 (N-O symmetrical). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 13.07 (s, 1H), 8.56 (s, 1H), 8.51-8.41 (m, 2H), 8.25 (d, J= 8.7 Hz, 1H), 8.14 (d, J=7.6 Hz, 1H), 8.08 (d, J= 8.0 Hz, 2H), 7.95 (d, J=8.0 Hz, 2H), 7.89 (t, J=7.6 Hz, 1H), 7.79 (d, J= 8.4 Hz, 1H), 3.76-3.65 (m, 1H), 2.58-2.50 (m, 2H), 1.85 (d, J=12.0 Hz, 2H), 1.72 (d, J=13.0 Hz, 2H), 1.52-1.49 (m, 1H), 1.11 (d, J=13.5 Hz, 1H), 0.93 (d, J=13.5 Hz, 2H). LC-MS m/z = 470.41 $[M+H]^+$.

#### 3.1.13 3-(3-cyclohexyl-2-(3-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl) benzamide (3i)

Light yellow solid product; MP: 188-192°C; Rf: 0.26 (TLC, Ethylacetate: n-hexane = 4: 1); Yield: 37%.

IR ($u_{max}$, $cm^{-1}$): 2933, 2856 (Ar. C-H), 1670 (C=O), 1654 (C=O), 1616 (C=N), 1589, 1577 (Ar. C=C), 1529 (N-O asymmetrical), 1479, 1344 (N-O symmetrical). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.54 (d, J=18.5 Hz, 2H), 8.44 (d, J=8.4 Hz, 1H), 8.32 (s, 1H), 8.25 (d, J= 10.1 Hz, 2H), 8.14 (d, J=7.7 Hz, 1H), 7.92 (ddd, J=25.5, 16.1, 8.0 Hz, 3H), 7.80 (d, J=8.5 Hz, 1H), 7.62 (t, J=7.6 Hz, 1H), 7.50 (s, 1H), 3.70-3.68 (m, 1H), 2.59-2.50 (m, 2H), 1.86 (d, J=12.3 Hz, 2H), 1.73 (d, J=12.8 Hz, 2H), 1.52 (d, J=12.9 Hz, 1H), 1.11 (d, J=13.4 Hz, 1H), 0.93 (d, J=13.9 Hz, 2H). LC-MS m/z = 469.44 $[M+H]^+$.

#### 3.1.14 3-cyclohexyl-6-(3-hydroxyphenyl)-2-(3-nitrophenyl) quinazolin-4(3*H*)-one (3j)

Off white solid product; MP: 203-207°C; Rf: 0.34 (TLC, Ethylacetate: n-hexane = 4: 1); Yield: 53%.

IR ($u_{max}$, $cm^{-1}$): 3350 (O-H), 2926, 2856 (Ar. C-H), 1681 (C=O), 1658, 1616 (C=N), 1587 (Ar. C=C), 1537 (N-O asymmetrical), 1473, 1344 (N-O symmetrical). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.66 (s,1H), 8.54 (s, 1H), 8.44 (d, J=8.4 Hz, 1H), 8.34 (s, 1H), 8.11 (t, J=8.4 Hz, 2H), 7.87 (t, J=8.1 Hz, 1H), 7.74 (d, J=8.4 Hz, 1H), 7.33 (t, J=7.9 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.14 (s, 1H), 6.84 (d, J= 8.0 Hz, 1H), 3.70-3.68 (m, 1H), 2.59-2.50 (m, 2H), 1.84 (d, J=12.3 Hz, 2H), 1.72 (d, J=13.0 Hz, 2H), 1.51 (d, J=12.5 Hz, 1H), 1.16-1.09 (m, 1H), 0.93 (d, J=13.5 Hz, 2H). LC-MS m/z = 442.7 $[M+H]^+$.

#### 3.1.15 3-benzyl-6-(3-hydroxyphenyl)-2-(3-nitrophenyl) quinazolin-4(*3H*)-one (3k)

Light yellow solid product; MP: 212-216°C; Rf: 0.34 (TLC, Ethylacetate: n-hexane = 4: 1); Yield: 49%.

IR ($u_{max}$, $cm^{-1}$): 3250 (O-H), 3084 (Alkane C-H), 1653 (C=O), 1614 (C=N), 1577 (Ar. C=C), 1525 (N-O asymmetrical), 1479, 1344 (N-O symmetrical). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.67 (s, 1H), 8.41 (s, 1H), 8.34 (d, J=8.4 Hz, 1H), 8.25 (s, 1H), 8.17 (d, J=8.6 Hz, 1H), 7.85 (dd, J=23.1, 8.1 Hz, 2H), 7.71 (t, J=8.0 Hz, 1H), 7.34 (t, J=7.8 Hz, 1H), 7.31-7.15 (m, 5H), 6.94 (d, J=6.6 Hz, 2H), 6.85 (d, J=8.1 Hz, 1H), 5.21 (s, 2H). LC-MS m/z = 450.10 $[M+H]^+$.

#### 3.1.16 3-cyclohexyl-2-(3-nitrophenyl)-6-(2-(trifluoromethyl)phenyl)quinazolin-4(3*H*)-one (3l)

Off white solid product; MP: 192-196°C; Rf: 0.42 (TLC, Ethylacetate: n-hexane = 1: 4); Yield: 52%.

IR ($u_{max}$, $cm^{-1}$): 2933, 2862 (Ar. C-H), 1666 (C=O), 1616 (C=N), 1558 (Ar. C=C), 1533 (N-O asymmetrical), 1456, 1346 (N-O symmetrical), 1315 (C-F), 1168 (C-F), 1118 (C-F). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.58 (t, J=1.9 Hz, 1H), 8.44 (dd, J=8.3, 2.3 Hz, 1H), 8.15 (d, J=7.7 Hz, 1H), 8.07 (d, J=2.0 Hz, 1H), 7.89 (dd, J=8.0, 7.5 Hz, 2H), 7.84-7.65 (m, 4H), 7.50 (d, J=7.6 Hz, 1H), 3.70-3.65 (m, 1H), 2.54-2.50 (m, 2H), 1.85 (d, J=12.1 Hz, 2H), 1.71(d, J=13.0 Hz, 2H), 1.49 (d, J=12.9 Hz, 1H), 1.07 (t, J=12.9 Hz, 1H), 0.91 (dd, J=12.2, 11.7 Hz, 2H). LC-MS m/z = 494.37 $[M+H]^+$.

#### 3.1.17 3-benzyl-2-(3-nitrophenyl)-6-(2-(trifluoromethyl)phenyl)quinazolin-4(3*H*)-one (3m)

Off white solid product; MP: 201-205°C; Rf =0.44 (TLC, Ethylacetate: n-hexane = 1: 4); Yield: 42%.

IR ($u_{max}$, $cm^{-1}$): 3035 (Alkane C-H), 2953 (Ar. C-H), 1674 (C=O), 1618 (C=N), 1589 (Ar. C=C), 1533 (N-O asymmetrical), 1479, 1348 (N-O symmetrical), 1313 (C-F), 1172 (C-F), 1112 (C-F). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.36 (dd, J=8.4, 2.3 Hz, 1H), 8.29 (s, 1H), 8.16 (d, J=1.9 Hz, 1H), 7.86 (ddt, J=27.0, 11.4, 7.7 Hz, 5H), 7.72 (q, J=7.5 Hz, 2H), 7.55 (d, J=7.5 Hz, 1H), 7.23 (d, J=6.3 Hz, 3H), 7.00-6.93 (m, 2H), 5.19 (s, 2H). LC-MS m/z = 502.26 $[M+H]^+$.

### 3.2 Prediction of Drug Likeness and Absorption

Biological activity being the function of the complex influence of many molecular descriptors in a drug, highlighting the effect of some individual parameters makes it possible to estimate the drug-likeness of newly synthesized molecules. There are several strategies for defining drug-like properties, Lipinski's rule is most commonly preferred. It states that to be drug-like, a candidate should have less than five hydrogen bond donors (HBD), less than 10 hydrogen bond acceptors (HBA), a molecular

weight of less than 500 Da, and a partition coefficient log P of less than 5. It aims to highlight possible bioavailability problems if two or more properties are violated [30,31]. Out of synthesized targets **(3a to 3m),** all molecules follow Lipinski's rule except **3c** and **3m** which violate two criteria of Log P and molecular weight. However, they need be explored during formulation development and bioavailability study. Moreover, all synthesized targets **(3a to 3m)** show good percentage of absorption. Results of calculated molecular properties and % absorption have been summarized in Table 1 and Table 2.

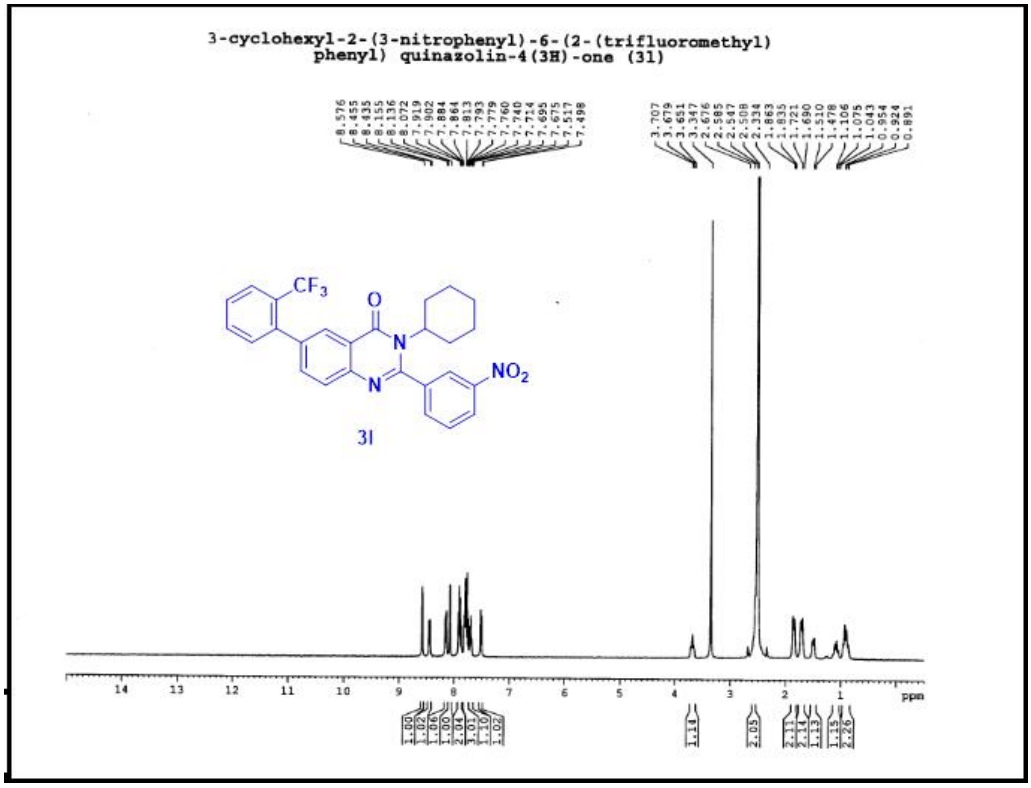


**Fig. 3. $^{1}$H-NMR Spectra of 3-cyclohexyl-2-(3-nitrophenyl)-6-(2-(trifluoromethyl)phenyl)quinazolin-4(3*H*)-one (3l)**

**Table 1. Drug likeness properties**

| Compounds | Log P | MW | nON | nOHNH | nrotb | nviol |
|---|---|---|---|---|---|---|
| **3a** | 5.02 | 397.43 | 6 | 0 | 5 | 1 |
| **3b** | 8.06 | 494.38 | 6 | 0 | 4 | 1 |
| **3c** | 7.75 | 502.36 | 6 | 0 | 5 | 2 |
| **3d** | 6.06 | 439.50 | 6 | 0 | 5 | 1 |
| **3e** | 6.63 | 447.49 | 6 | 0 | 6 | 1 |
| **3f** | 6.40 | 478.46 | 9 | 0 | 6 | 1 |
| **3g** | 7.15 | 467.91 | 6 | 0 | 5 | 1 |
| **3h** | 6.69 | 469.50 | 8 | 1 | 5 | 1 |
| **3i** | 5.57 | 468.51 | 8 | 2 | 5 | 1 |
| **3j** | 6.28 | 441.49 | 7 | 1 | 4 | 1 |
| **3k** | 5.97 | 449.47 | 7 | 1 | 5 | 1 |
| **3l** | 7.63 | 493.49 | 6 | 0 | 5 | 1 |
| **3m** | 7.32 | 501.46 | 6 | 0 | 6 | 2 |

*MW: molecular weight, nON: number of hydrogen bond acceptors, nOHNH: number of hydrogen bond donors, nrotb: number of rotatable bonds nviol: number of violations*

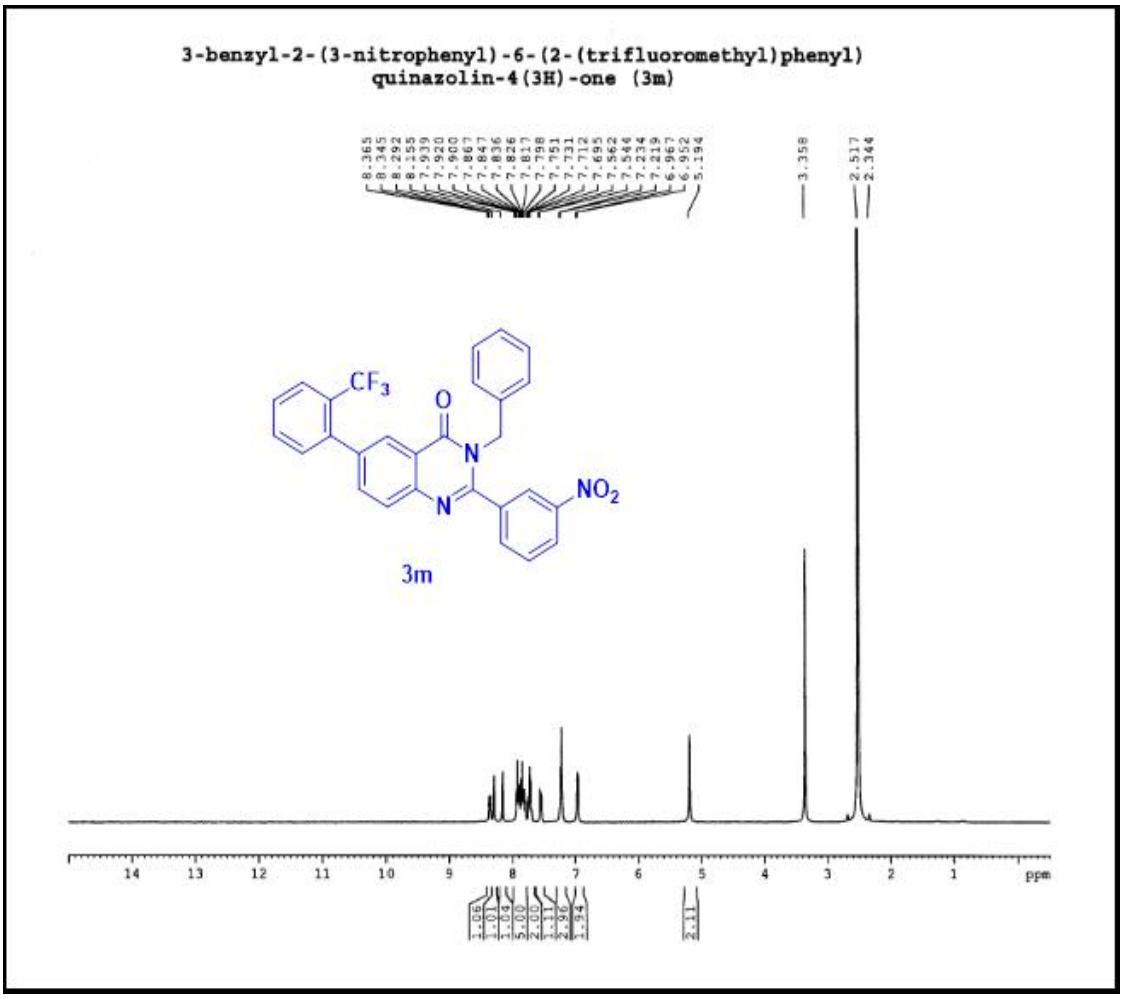


**Fig. 4. $^{1}$H-NMR Spectra of 3-benzyl-2-(3-nitrophenyl)-6-(2-(trifluoromethyl)phenyl)quinazolin-4(3*H*)-one (3m)**

**Table 2. Percentage of absorption**

| Compounds | MV | TPSA | %abs |
|---|---|---|---|
| **3a** | 350.77 | 80.72 | 81.15 |
| **3b** | 411.45 | 80.72 | 81.15 |
| **3c** | 409.66 | 80.72 | 81.15 |
| **3d** | 373.30 | 80.72 | 81.15 |
| **3e** | 399.39 | 80.72 | 81.15 |
| **3f** | 405.93 | 126.55 | 65.34 |
| **3g** | 396.13 | 80.72 | 81.15 |
| **3h** | 411.38 | 118.02 | 68.28 |
| **3i** | 414.65 | 123.81 | 66.29 |
| **3j** | 392.39 | 100.95 | 74.17 |
| **3k** | 390.61 | 100.95 | 74.17 |
| **3l** | 415.67 | 80.72 | 81.15 |
| **3m** | 413.89 | 80.72 | 81.15 |

*MV: molecular volume, TPSA: Total Polar Surface Area, %abs: percentage of absorption.*

**Table 3. Pancreatic lipase inhibition (IC50 values)**

| Compounds | IC50 (µg/mL) Mean ± SEM | Compounds | IC50 (µg/mL) Mean ± SEM |
|---|---|---|---|
| **3a** | 19.72±0.87 | **3h** | 27.73±1.24 |
| **3b** | 48.85±1.67 | **3i** | 38.10±0.83 |
| **3c** | 34.81±0.87 | **3j** | 21.60±1.16 |
| **3d** | 31.33±1.31 | **3k** | 64.95±2.47 |
| **3e** | 69.81±1.78 | **3l** | 13.13±0.84 |
| **3f** | 30.87±2.12 | **3m** | 13.80±1.27 |
| **3g** | 20.27±1.86 | **Orlistat** | 12.72±0.97 |

*Mean ± S.E.M = Mean values ± Standard error of means*

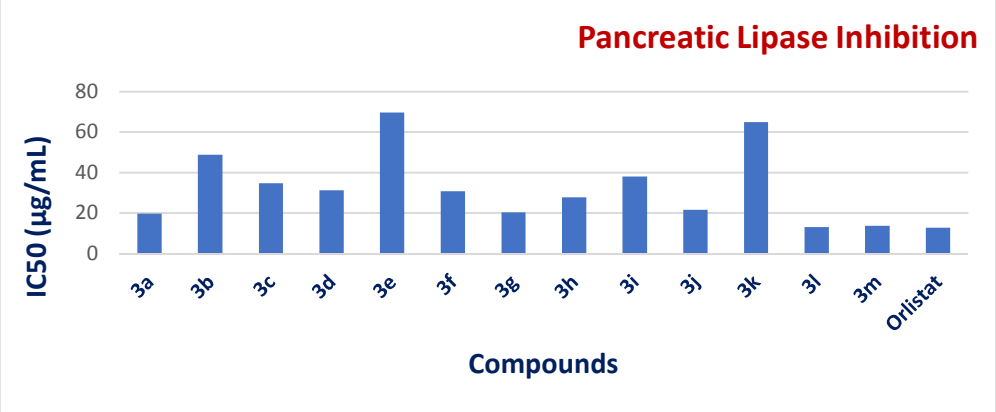


**Fig. 5. Pancreatic lipase inhibition**

### 3.3 Pancreatic Lipase Inhibitory Activity (Anti-Obesity Activity)

Compounds (**3a to 3m**) were tested for pancreatic lipase inhibition activity and results were compared with Orlistat (Positive control). The pancreatic lipase inhibitory effects of the test compounds were indicated by IC50 value in Table 3.

Orlistat prevents absorption of fat from human diet and thereby produces calorie intake. It works by inhibiting pancreatic lipase, an enzyme that breakdowns triglyceride in the intestine and in absence of this enzyme, triglycerides from the diet are prevented from being hydrolyzed into the absorbable free fatty acids and instead excreted unchanged and undigested [32].

Pancreatic lipase is an important lipolytic enzyme secreted into the duodenum via duct system of pancreas. It plays a significant role in dietary trigycerol absorption. Pancreatic lipase hydrolyses triglycerols to monoacyl glycerols and fatty acids and it accounts for the hydrolysis of 50-70% of total dietary fats. The synthesized compounds studied here may probably inhibit digestion and absorption of dietary lipids through an inhibitory action on pancreatic lipase and therefore they can be further developed as potent anti-obesity agents. $IC_{50}$ value of Orlistat (positive control) was found to be 12.72±0.97 µg/mL. From all the tested compounds, **3l** and **3m** exhibited $IC_{50}$ Value of 13.13±0.84 µg/mL and 13.80±1.27 µg/mL respectively, suggesting their potent pancreatic lipase inhibitory functions comparable to the standard Orlistat.

## 4. CONCLUSION

Quinazolin-4(3H)-one derivatives constitute an important class of heterocycles with diverse pharmacological activities. All the title compounds **(3a-3m)** were synthesized, characterized, and evaluated for their drug likeness, absorbance and pancreatic lipase inhibitory activity. Two most potent compounds **3l** and **3m** exhibited IC50 value of 13.13±0.84 µg/mL and 13.80±1.27 µg/mL respectively for pancreatic lipase inhibition which is analogous to the orlistat, a US FDA approved drug for the treatment of obesity. Two molecules **3l** and **3m**

can be further evaluated for their effectiveness to treat obesity disorder.

## CONSENT AND ETHICAL APPROVAL

It is not applicable.

## AVAILABILITY OF DATA AND MATERIAL

All data and material are available upon request.

## SUPPLEMENTARY MATERIAL

Supplementary materials is available in this Link Available:https://journaljpri.com/index.php/JPRI/libraryFiles/downloadPublic/13

## COMPETING INTERESTS AND DISCLAIMER

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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