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

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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.

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ABSTRACT

Aim: A series of novel quinazolinone derivate 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 quinazolinone-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 quinazolinone-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 likensness, 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
have reasonably good molecular properties except 3c and 3m which violate two criteria for Lipinski’s rule. Whereas, Compounds 3l and 3m showed IC\textsubscript{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 triglycerol 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\textsubscript{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 monooamine 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 \(\text{o-aminobenzamides} \) intermediate [13], using various catalysts like graphite at 220 °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

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**Fig. 1. Some quinazolinone drugs**

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reactions which utilize reagents like triphenylphosphine [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 LiClO₄ 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
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 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-methylumbelliferol 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 CaCl₂ (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 fluorometric 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%.

1H NMR (400 MHz, DMSO-d6): δ 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%.

1H NMR (400 MHz, DMSO-d6): δ 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(3H)-one (2a)

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

1H NMR (400 MHz, DMSO-d6): δ 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), 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(3H)-one (2b)

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

1H NMR (400 MHz, DMSO-d6): δ 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(3H)-one (3a)

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

IR (υmax, 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). 1H NMR (400 MHz, DMSO-d6): δ 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(3H)-one (3b)

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

IR (υmax, 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). 1H NMR (400 MHz, DMSO-d6): δ 8.56 (s, 1H), 8.45 (s, 1H), 8.43 (s, 1H), 8.24 (d,
3.1.7 3-benzyl-6-(3,5-dichlorophenyl)-2-(3-nitrophenyl)quinazolin-4(3H)-one (3c)

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

IR (ν<sub>max</sub>, cm<sup>-1</sup>): 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). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 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 = 494.34 [M+H]<sup>+</sup>.

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

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

IR (ν<sub>max</sub>, cm<sup>-1</sup>): 3093 (Alkane C-H), 1676 (C=O), 1618 (C=N), 1581 (Ar. C=C), 1529 (N-O asymmetrical), 1487, 1350 (N-O symmetrical), <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 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]<sup>+</sup>.

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

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

IR (ν<sub>max</sub>, cm<sup>-1</sup>): 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), <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 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]<sup>+</sup>.

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 (ν<sub>max</sub>, cm<sup>-1</sup>): 3088 (Alkane C-H), 2962, 2852 (Ar. C-H), 1683 (C=O), 1616 (C=N), 1575 (Ar. C=C), 1525 (N-O asymmetrical), 1500, 1348 (N-O symmetrical). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 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]<sup>+</sup>.

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

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

IR (ν<sub>max</sub>, cm<sup>-1</sup>): 1683 (C=O), 1616 (C=N), 1558 (Ar. C=C), 1527 (N-O asymmetrical), 1475, 1350 (N-O symmetrical), 821(C-Cl). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 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]<sup>+</sup>.

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 (ν<sub>max</sub>, cm<sup>-1</sup>): 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). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 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]<sup>+</sup>.
3.1.13 3-(3-cyclohexyl-2-(3-nitrophenoxy)-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 (\(\nu_{\text{max}}\), 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-nitrophenoxy) quinazolin-4(3H)-one (3j)

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

IR (\(\nu_{\text{max}}\), 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=12.6 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-nitrophenoxy) 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 (\(\nu_{\text{max}}\), 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-nitrophenoxy)-6-(2-(trifluoromethyl)phenyl) quinazolin-4(3H)-one (3l)

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

IR (\(\nu_{\text{max}}\), 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-nitrophenoxy)-6-(2-(trifluoromethyl)phenyl) quinazolin-4(3H)-one (3m)

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

IR (\(\nu_{\text{max}}\), 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 (dd, 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. ¹H-NMR Spectra of 3-cyclohexyl-2-(3-nitrophenyl)-6-(2-(trifluoromethyl)phenyl)quinazolin-4(3H)-one (3l)](image)

**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*
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*

### 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 triglycerol 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. IC50 value of Orlistat (positive control) was found to be 12.72±0.97 µg/mL. From all the tested compounds, 3l and 3m exhibited IC50 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

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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.

REFERENCES

1. Lambat TL, Chopra PKPG, Mahmood SH. Microwave: A Green Contrivance for the Synthesis of N-Heterocyclic Compounds. Curr Org Chem. 2020;24(22):2527-2554.

2. Rudolph J, Esler WP, O’Connor S, Coish PDG, Wickens PL, Brands M, et al. Quinazoline derivatives as orally available ghrelin receptor antagonists for the treatment of diabetes and obesity. J Med Chem. 2007;50(21):5202-5216.

3. Sinha S, Srivastava M. Biologically active quinazolines. Prog Drug Res. 1994;43:143.

4. De Laszlo SE, Quagliato CS, Greenlee WJ, Patchett AA, Chang RSL, Lotti VJ et al. A potent, orally active, balanced affinity angiotsensin II AT1 antagonist and AT2 binding inhibitor. J Med Chem. 1993;36:3207-3210.

5. Liverton NJ, Armstrong DJ, Claremon DA, Remy DC, Baldwin JJ, Lynch RJ, et al. Nonpeptide glycoprotein ib/iiia inhibitors: substituted quinazolinediones and quinazolinones as potent fibrinogen receptor antagonists. Bioorganic Med Chem Lett. 1998;8:483.

6. Zhang W, Mayer JP, Hall SE, Weigel JA. A polymer-bound iminophosphorane approach for the synthesis of quinazolines. J Comb Chem. 2001;3:255-256.

7. Gopalsamy A, Yang H. Combinatorial synthesis of heterocycles:solid-phase synthesis of 2-amino-4(1H)-quinazolinone derivatives. J Comb Chem. 2000;2:378-381.

8. Vasantha M, Satyanarayana RP. Synthesis and anti-diabetic activity of some 3-methylquinazolin-4(3H)-one derivatives. Int J ChemTech Res. 2014;6:5647-5652.

9. Fawzia MR, Amr YE, Soad MA, Aida MI, Mona AM. The anti-hyperlipidemic activities of 4(3H) quinazoline and two halogenated derivatives in rats. Lipids in Health and Disease. 2005;4:22.

10. Santosh NM, Akash DP, Pritam ND, Nikhil SS, Pankaj BM. Design, synthesis and in vivo screening of some novel quinazoline analogs as anti-hyperlipidemic and hypoglycemic agents. Bioorganic Med Chem Lett. 2016;26(2):272-276.

11. Mohammad A. Chemical characteristics, synthetic methods and biological potential of quinazoline and quinazolinone derivatives. Int J Med Chem; 2014. Accessed on 15 March 2021.

Available:https://www.hindawi.com/journals/ijmc/2014/395637/

12. Mankun W, Wei-Ming C, Rui W, Qin Y, Zhihong D, Yiyuan P. Quinazoline and quinazolinone derivatives: Synthesis and comparison of inhibitory mechanisms on α-glucosidase. Bioorganic Med Chem Lett. 2017;25(4):1303-1308.

13. Alexandre FR, Berecibar A, Besson T. Microwave-assisted niementowski reaction. Back to the roots. Tetrahedron Lett. 2002;43:3911-3913.

14. Mariade FP, Valérie T, Thierry B. Synthesis of novel 2,3-substituted quinazolin-4-ones by condensation of alkyl or aromatic diamines with 5-(N-arylimino)-4-chloro-5H-1,2,3-dithiazoles. Tetrahedron. 2006;63:847-854.

15. Mariade FP, Laurent P, Jean G, Jean-Michel L, Christian J, Valérie T, Thierry B. Efficient synthesis of novel pentacyclic 6,7-dihydro-5a,7a,13,14-tetraaza-pentaphene-5,8-diones. Tetrahedron Lett. 2005;46:3445-3447.
16. Kabri Y, Gellisa A, Vanelle P. Microwave-assisted synthesis in aqueous medium of new quinazoline derivatives as anticancer agent precursors. Green Chem. 2009;11:201-208.

17. Muthu KK, Rajeshwar RJ, Aparna SC, Trupti SC, Riyaj ST, Kumar VS. The synergy of combined use of DMSO and bronsted acid (ionic liquid) as a catalyst. Green and Sustainable Chemistry. 2011;1:12-18.

18. Lambat TL. Scolecite as novel heterogeneous catalyst for an efficient microwave assisted synthesis of 7-Aryl-6H-benzo[H][1,3]dioxolo[4,5-b]xanthene-5,6 (7H)-dione analogues via multi-component reaction. Int J Appl Biol Pharm. 2017;8(4):11-18.

19. Lambat TL, Deo SS. Sulphamic acid:an efficient and green synthesis of 2-[3-(4-3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridine-3-(2H)-one hydrochloride and its derivatives. Der Pharmacia Lett. 2014;6(3):218-224.

20. Sugimori T, Okawa T, Eguchi S, Yashima E, Okamoto Y. The first total synthesis of (−)-benzomalvin A via intramolecular aza-Wittig reactions. Chem Lett. 1997;869-870.

21. Juan AB, Pilar MF, Raul O, Pedro M. Preparation of fused tetracyclic quinazolinones by combinations of aza-Wittig methodologies and Cul catalyzed heteroarylation processes. Eur J Org Chem. 2009;2009:2490-2504.

22. Chang X, Hong XL, Ming GL, Ming WD. Efficient synthesis of 4(3H)-quinazolinones using a soluble polymeric support. Chin Chem Lett. 2008;19:505-508.

23. Muhammad S, Jultia O, Peter L, Matthias B, Xiao-Feng W. Oxidative synthesis of quinazolinones and benzothiadiazine 1,1-dioxides from 2-aminoenbenzamide and 2-aminoenbenzenesulfonamide with benzyl alcohols and aldehydes. RSC Advances. 2014;4:8-17.

24. Jianguang Z, Jie F. One-pot synthesis of quinazolinones via iridium-catalyzed hydrogen transfers. J Org Chem. 2011;76:7730-7736.

25. Jie F, Jianguang Z. Efficient syntheses of 2,3-disubstituted natural quinazolinones via iridium catalysis. Org Biomol Chem. 2012;10:2389-2391.

26. Hidekazu H, Yukari I, Hideharu S, Yuusaku Y. Pd-catalyzed benzylic C–H amidation with benzyl alcohols in water:A strategy to construct quinazolinones. J Org Chem. 2012;77:7046-7051.

27. Huamin W, Xiangxiang C, Fuhong X, Saiwen L, Guo-Jun D. Iron-catalyzed one-pot 2,3-diarylquinazolone formation from 2-nitrobenzamides and alcohols. Org Lett. 2013;15:4900-4903.

28. Calculation of Molecular Properties and Bioactivity Score. Accessed on 17 April 2021. Available:http://www.molinspiration.com/cgi-bin/properties

29. Masaaki N, Yuko F, Sumio A, Yoshiko T, Takashi I, Hiroshi S et al. Inhibitory effects of oolong tea polyphenols on pancreatic lipase in vitro. J Agric Food Chem. 2005;53:4593-4598.

30. Vaibhav S, Chandra SS. Synthesis, antimicrobial activity, drug Likeness and in silico toxicity study of some novel triazole derivatives. Int J Pharm Sci Drug Res. 2021;13(1):93-98.

31. Zlatkov A, Tsvetkova B, Andonova L, Peikov. Synthesis, structural analysis and drug-likeness estimation of some imidazole derivatives. In the Proceedings of the 2011 Pharmacia conference. 2011:58.

32. Ballinger A, Peikin S. Orlistat:Its current status as an anti-obesity drug. Eur J Pharmacol. 2002;440:109-117.

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