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Facile synthesis of diverse N-Acyl Anthranilamides and quinazolin-4-ones as HMG-CoA reductase inhibitor *via* Pd-catalyzed cascade reaction

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Abstract: This manuscript describes the design and synthesis of a series of diverse N-Acyl Anthranilamides and quinazolin-4-ones derivatives (**3a-3n, and 4a-4d**) inhibitors of HMG-CoA reductase for the treatment of hypercholesterolemia. A series of N-Acyl Anthranilamides and quinazolin-4-ones derivatives (**3a-3n, and 4a-4d**) were synthesized and their chemical structures were confirmed by 1 H, 13C NMR and mass spectral data. Analogs were optimized using structure-based design and physical property considerations resulting in the identification of 4b and 3d, a hepatoselective HMG-CoA reductase inhibitor with excellent acute and chronic efficacy in a vitro model.

Keywords: hypercholesterolemia, HMG-CoA reductase, Molecular docking, N-Acyl Anthranilamides and quinazolin-4-ones derivatives.

Introduction:

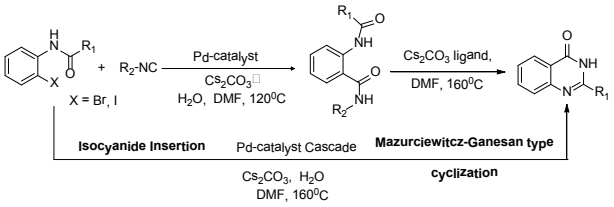
The development organometallic chemistry of cross-coupling reactions represents a pattern shift in chemical synthesis, and today synthetic chemists can willingly access C-C/C-N/C-O/C-S and other carbon-heteroatom bonds from a vast collection of starting compounds. Although we cannot understate the importance of these methods, the required pre-functionalization to

carry out these reactions adds cost and reduces the availability of the starting reagents. The Pd-catalyzed cascade reactions with C-C/C-N/C-O/C-S and other carbon-heteroatom bond formation have made a immense involvement to the current development of organic synthesis.[1]Recently, much attention has been paid toward the development of Pd-catalyzed insertion reactions, in which isocyanides is inserted between the two coupling partners due to the capability of Pd- metal complex to react with the π-system of isocyanide.[2]

on the other hand, isocyanides, which are isoelectronic with carbon monoxide, has been used as synthetic surrogates of CO in Pd-catalyzed tandem reaction due to the potential of transition metal complex to react with *л*-system of isocyanides. In this context, a broad range of heterocycles has been synthesized using isocyanides instead of CO in transition metal catalyzed tandem reactions.[3]

Recently, Ji et. al. accounted a Pd-catalyzed synthesis of isocoumarins and phthalides *via* isocyanide insertion.[4] We have also developed a diversity oriented synthesis of isoquinolines-one and isoindolinone via the ligand free Pd-catalyzed coupling cascade reaction with insertion of isocyanides into amide.[5,6] Inspired by the above literature and our previous report, we envisaged that the insertion of isocyanides into amide to synthesize substituted N-Acyl Anthranilamide and quinazolin-4-one derivatives might be possible (Scheme 1).

The atom-economical synthesis of N-acyl anthranilamides from readily available anilides and isocyanates is of significant practical utility given that this structural motif is found in numerous drugs and drug candidates[7](Figure 1). Anthranilamides are typically prepared from the corresponding anthranilic acids; however, this approach is inherently restricted by the limited selection of commercially available anthranilic acids[8]. Moreover, both N-acyl anthranilamides and enamine amides are poised to undergo cyclodehydration reactions to provide quinazolinone and pyrimidinone frameworks, which are also a common feature in approved drugs and drug candidates.[9]



Scheme 1. our approaches using isocyanides as a coupling partner

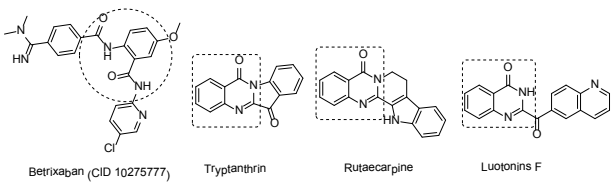


Figure 1. Some biologically active molecules and natural products containing N-Acyl anthranilamide, quinazolin-4-one motif.

Quinazolinone is a building block of naturally occurring alkaloids and utilized as a drug like scaffold in several natural products[10-14] (Trypanthrine, rutaecarpine and luotonin A, Figure 1), as these possess a wide range of biological activities including antitumor, anticonvulsant,[15] antiviral,[16] antiinflammatory, analgesic,[17] antimicrobial,[18] antifungal,[19] antimalarial, antidiabetic,[20] cytotoxicity[21] and angiotensin II AT1 receptor antagonists.[22] Recently we have developed an efficient and facile methodology for the preparation of this privileged quinazolinone scaffold.[23]

It is generally recognized that hypercholesterolemia and high levels of serum LDL-cholesterol contribute significantly to the progression of atherosclerosis[24] which is the leading cause of cardiovascular diseases. Liver enzyme 3-hydroxy-3-methylglutaryl-

coenzyme A (HMG-CoA) reductase (HMGR) catalyzes the formation of mevalonate, the key step in the biosynthesis of cholesterol and isoprenoids.[25] Therefore, inhibition of this enzyme has proven to be the most efficient therapy for hyperlipidemia.[26]

Owing to the synthetic importance of N-Acyl Anthranilamide and quinazolin-4-one, based on our continuing interest towards the synthesis of biologically important heterocycles using isocyanide based chemistry, herein, we disclose a Pd-catalyzed tandem C-C/C-N coupling reaction affording a variety of functionalized N-Acyl Anthranilamide and quinazolin-4-one derivatives in high yields using amide and isocyanides as coupling partner. Here we are also going to disclose the (HMG-CoA) reductase inhibitory potential of these compounds.

Experimental

General information:

All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with 300 MHz spectrometers for ^{1}H NMR and 50 MHz for ^{13}C NMR on Bruker Supercon Magnet Avance DRX-300 spectrometers in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, coupling constant *J* in Hz.). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad singlet (br s). Mass spectra and HRMS were taken in the ESI positive ion mode. The reaction progress was monitored by thin layer chromatography (TLC) on pre-coated silica gel plates. Column chromatography was performed over Merck silica gel (230-400 flash). All compounds were characterized by TLC, ^{1}H NMR and ^{13}C NMR, MS and HRMS.

General Procedure for the synthesis of substituted isoindolines 3a-n:

Amide **3** (1 mmol), isocyanide **2** (1.2mmol), $Pd(OAc)_2$ (10 mol %), Cs_2CO_3 (2 mmol.), PPh_3(10 mol %) and DMF/$H_2$0 (10/1 ,2 mL) as a solvent were added in a 10 mL reaction glass vial containing a stirring bar under the nitrogen atmosphere, the vial was sealed tightly with a Teflon cap and placed in microwave cavity for 15 min at a pre-selected temperature of 120 °C. After completion of the reaction as indicated by TLC, the resulting mixture was filtered through a pad of celite, and the celite was rinsed with EtOAc. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluent: hexane/ EtOAc) affording the corresponding coupling product **3a-n** in 85-71% yields.

General Procedure for the synthesis of substituted isoindolines 4a-d:

Amide **3** (1 mmol), isocyanide **2** (1.2mmol), $Pd(OAc)_2$ (10 mol %), Cs_2CO_3 (2 mmol.), PPh_3(10 mol %) and DMF/$H_2$0 (10/1 ,2 mL) as a solvent were added in a 10 mL reaction glass vial containing a stirring bar under the nitrogen atmosphere, the vial was sealed tightly with a Teflon cap and placed in microwave cavity for 45 min at a pre-selected temperature of 160 °C. After completion of the reaction as indicated by TLC, the resulting mixture was filtered through a pad of celite, and the celite was rinsed with EtOAc. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluent: hexane/ EtOAc) affording the corresponding coupling product **4a-d** in 84-71% yields.

Characterization of compound-2-benzamido-N-tert-butylbenzamide (3a) -

Solid, Yield = 76%, mp = 143-146 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3425, 2946, 2324, 1627, 1106, 759, ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.95 (br s, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.06-8.04 (m, 2H), 7.58-7.44 (m, 5H), 7.09 (t, *J* = 7.2 Hz, 1H),

6.16 (br s, 1H), 1.52 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 169.0, 165.5, 139.5, 134.8, 132.2, 131.7, 128.7, 127.4, 126.4, 122.7, 122.3, 121.6, 52.2, 28.7 ppm, HRMS (ESI) Calcd. for $C_{18}H_{20}N_2O_2$ $[M+H]^+$ 297.1525 Found 297.1595.

2-benzamido-N-(2,4,4-trimethylpentan-2-yl) benzamide (3b) -

Solid, Yield = 71%, mp = 123-125 ^{0}C FT-IR (KBr) ν (cm^{-1}): 3413, 2948, 2356, 1647, 1026, 762, ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.9 (br s, 1H), 8.76 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 6.8 Hz, 2H), 7.58-7.42 (m, 5H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.20 (br s, 1H), 1.92 (s, 2H), 1.57 (s, 6H), 1.07 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 168.8, 165.4, 139.3, 134.8, 132.0, 131.7, 128.7, 127.3, 126.3, 122.8, 122.7, 121.7, 56.1, 51.5, 31.7, 31.5, 29.1 ppm, HRMS (ESI) Calcd. for $C_{22}H_{28}N_2O_2$ $[M+H]^+$ 353.2151 Found 353.2221.

.**2-benzamido-N-cyclohexylbenzamide (3c) -**Solid, Yield = 83%, mp = 121-123 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3434, 2903, 2322, 1627, 1146, 789, ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.0 (br s, 1H), 8.77 (d, *J* = 8.1 Hz, 1H), 8.05 (d, *J* = 5.7 Hz, 2H), 7.55-7.49 (m, 5H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.43 (br s, 1H), 4.00-3.97 (m, 1H), 2.07-2.04 (m, 2H), 1.81-1.67 (m, 3H), 1.51-1.21 (m, 5H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): 168.3, 165.5, 139.7, 134.8, 132.4, 131.8, 128.7, 127.3, 126.6, 122.7, 121.5, 121.0, 48.8, 33.0, 25.4, 24.9 ppm, HRMS (ESI) Calcd. for $C_{20}H_{22}N_2O_2$ $[M+H]^+$ 323.1681 Found 323.1751

N-(2-(tert-butylcarbamoyl)phenyl)-3,4,5-trimethoxybenzamide (3d) -

Solid, Yield = 78%, mp = 103-105 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3315, 2903, 2334, 1605, 1106, 769, ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.1 (br s, 1H), 8.79 (d, *J* = 8.4, 1H), 7.51-7.43 (m, 2H), 7.32 (s, 2H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.13 (br s, 1H), 3.97 (s, 6H), 3.92 (s, 3H), 1.49 (s, 9H) ppm.169.3, 165.2, 153.3, 141.2, 140.1, 132.6, 130.4, 126.6, 122.8, 121.7, 121.4, 104.8, 61.1, 56.3, 52.4, 28.9 ppm, HRMS (ESI) Calcd. for $C_{21}H_{26}N_2O_5$ $[M+H]^+$ 387.1842 Found 387.1917.

N-(2-(cyclohexylcarbamoyl)phenyl)-3,4,5-trimethoxybenzamide (3e) -

Solid, Yield = 75%, mp = 113-115 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3422, 2913, 2304, 1627, 1026, 749, ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.1 (s, 1H), 8.88-8.47 (m, 1H), 7.54-7.48 (m, 2H), 7.30 (s, 2H), 7.11 (t, *J* = 9.6 Hz, 1H), 6.28 (br s, 1H), 3.98 (s, 6H), 3.93 (s, 3H), 2.05-2.02 (m, 2H), 1.80-1.66 (m, 3H), 1.49-1.20 (m, 5H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): 168.3, 165.2, 153.2, 141.0, 139.8, 132.5, 130.3, 126.4, 122.7, 121.3, 120.9, 104.7, 60.9, 56.2, 48.8, 32.9, 25.4, 24.8 ppm, HRMS (ESI) Calcd. for $C_{23}H_{28}N_2O_5$ $[M+H]^+$ 413.1998 Found 413.2073.

N-tert-butyl-2-(4-methoxybenzamido) benzamide (3f) -

Solid, Yield = 83%, mp = 123-125 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3315, 2947, 2314, 1657, 1166, 783, ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.78 (s, 1H), 8.69 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.44-7.39 (m, 2H), 7.00-6.94 (m, 3H), 6.29 (br s, 1H), 3.86 (s, 3H), 1.50 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 169.3, 165.2, 162.6, 139.7, 132.2, 129.4, 127.4, 126.8, 122.6, 122.4, 121.6, 114.1, 55.6, 52.3, 28.7 ppm, HRMS (ESI) Calcd. for $C_{19}H_{22}N_2O_3$ $[M+H]^+$ 327.1630 Found 327.1705..

N-tert-butyl-2-(4-fluorobenzamido) benzamide (3g) -

Solid, Yield = 76%, mp = 128-130 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3407, 2923, 2304, 1627, 1026, 765, ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.9 (s, 1H), 8.72 (d, *J* = 8.4, 1H), 8.05-8.02 (m, 2H), 7.49-7.42 (m, 2H), 7.20 (t, *J* = 8.4 Hz, 2H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.19 (br s, 1H), 1.50 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 169.2, 164.5, 139.7, 132.4, 131.3, 131.2, 130.0, 129.9, 126.7, 123.0, 122.2, 121.7, 116.0, 115.8, 52.4, 28.9 ppm, HRMS (ESI) Calcd. for $C_{18}H_{19}FN_2O_2$ $[M+H]^+$ 315.1431 Found 315.1506.

N-tert-butyl-2-(3-chlorobenzamido) benzamide (3h) -
Solid, Yield = 82%, mp = 133-135 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3435, 2933, 2344, 1648, 1121, 749, ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.0 (s, 1H), 8.69 (s, *J* = 8.4 Hz, 1H), 8.03 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.53-7.42 (m, 4H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.33 (br s, 1H), 1.53 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 169.2, 164.3, 139.3, 136.9, 135.1, 132.3, 131.9, 130.2, 128.3, 126.8, 125.2, 123.2, 122.4, 121.7, 52.4, 28.9 ppm, HRMS (ESI) Calcd. for $C_{18}H_{19}ClN_2O_2$ $[M+H]^+$ 331.1135 Found 331.1212.

2-benzamido-N-tert-butyl-3,5-dimethylbenzamide (3i) -
Solid, Yield = 79%, mp = 106-108 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3415, 2903, 2214, 1617, 1123, 789, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 8.16 (d, *J* = 7.5 Hz, 2H), 7.58-7.46 (m, 3H), 7.00 (s, 1H), 6.95 (s, 1H), 6.50 (br s, 1H), 2.25 (s, 3H), 2.19 (s, 3H), 1.25 (s, 9H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 169.2, 167.4, 136.6, 136.5, 135.4, 133.8, 132.6, 131.7, 130.3, 128.4, 127.8, 125.3, 51.6, 28.4, 20.8, 18.4 ppm, HRMS (ESI) Calcd. for $C_{20}H_{24}N_2O_2$ $[M+H]^+$ 325.1838 Found 325.1912.

N-tert-butyl-2-butyramido-3,5-dimethylbenzamide (3j) -
Solid, Yield = 77%, mp = 144-146 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3410, 2940, 2334, 1608, 1174, 761, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.93 (s, 1H), 6.96 (d, *J* = 10.5 Hz, 2H), 6.37 (br s, 1H), 2.38 (t, *J* = 7.2 Hz, 3H), 2.23 (s, 3H), 2.12 (s, 3H), 1.87-1.72 (m, 2H), 1.41 (s, 9H), 1.04 (t, *J* = 6.6 Hz, 3H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$):173.2, 169.2, 136.2, 136.1, 134.7, 132.7, 130.3, 125.2, 51.6, 38.7, 28.5, 20.7, 19.4, 18.4, 14.0 ppm, HRMS (ESI) Calcd. for $C_{17}H_{26}N_2O_2$ $[M+H]^+$ 291.1994 Found 291.2070.

N-tert-butyl-2-butyramidobenzamide (3k) -Solid, Yield = 81%, mp = 113-115 ^{0}C , FT-IR (KBr) ν (cm^{-1}): 3411, 2913, 2304, 1637, 1120, 782, ^{1}H NMR (400 MHz, $CDCl_3$): 10.8 (br s, 1H), 8.4 (s, 1H), 7.39 (t, *J* = 5.4 Hz, 2H), 7.00 (s, *J* = 5.4 Hz, 1H), 6.16 (br s, 1H), 2.35 (t, *J* = 7.2 Hz, 2H), 1.76 (t, *J* = 7.2 Hz, 2H), 1.45 (s, 9H), 1.29-1.26 (m, 2H), 1.02-0.96 (m, 3H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): 172.1, 169.0, 139.2, 132.1, 126.7, 122.6, 122.4, 121.7, 52.2, 40.5, 28.9, 19.2, 13.9 ppm, HRMS (ESI) Calcd. for $C_{15}H_{22}N_2O_2$ $[M+H]^+$ 263.1681 Found 263.1757.

N-tert-butyl-2-pentanamidobenzamide (3l) -
Solid, Yield = 78%, mp = 122-124 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3422, 2918, 2319, 1602, 1066, 765, ^{1}H NMR (400 MHz, $CDCl_3$): 10.8 (s, 1H), 8.52 (d, *J* = 8.4 Hz, 1H), 7.51-7.36 (m, 2H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.16 (br s, 1H), 2.40 (t, *J* = 7.6 Hz, 2H), 1.76-1.64 (m, 2H), 1.48 (s, 9H), 1.45-1.36 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): 172.1, 168.8, 139.1, 131.9, 126.4, 122.4, 122.2, 121.5, 52.0, 38.1, 28.7, 27.6, 22.3, 13.7 ppm, HRMS (ESI) Calcd. for $C_{16}H_{24}N_2O_2$ $[M+H]^+$ 277.1838 Found 277.1904.

N-tert-butyl-2-pivalamidobenzamide (3m) -
Solid, Yield = 85%, mp = 107-109 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3411, 2903, 2214, 1614, 1146, 769, ^{1}H NMR (400 MHz, $CDCl_3$): 10.9 (br s, 1H), 8.53 (t, *J* = 4.8 Hz, 1H), 7.43-7.37 (m, 2H), 7.04-7.00 (m, 1H), 6.05 (br s, 1H), 1.48 (s, 9H), 1.32 (s, 9H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): 177.5, 169.0, 139.1, 131.7, 126.2, 123.0, 122.4, 121.6, 52.0, 31.5, 28.6, 27.5 ppm, HRMS (ESI) Calcd. for $C_{16}H_{24}N_2O_2$ $[M+H]^+$ 277.1838 Found 277.1905.

2-pivalamido-N-(2,4,4-trimethylpentan-2-yl) benzamide (3n) –
Solid, Yield = 79%, mp = 127-129 ^{0}C FT-IR (KBr) ν (cm^{-1}): 3348, 2947, 2304, 1619, 1026, 749, ^{1}H NMR (400 MHz, $CDCl_3$): 10.9 (br s, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 7.45-7.36 (m, 2H), 7.06 (t, *J* = 7.2 Hz, 1H), 5.98 (br s, 1H), 1.90 (s, 2H), 1.53 (s, 6H), 1.33 (s, 9H), 1.06 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$): 177.5, 168.7,

139.1, 131.7, 126.0, 123.2, 122.5, 121.7, 56.0, 51.3, 31.5, 29.2, 27.5, 22.6, 14.0 ppm, HRMS (ESI) Calcd. for $C_{22}H_{32}N_2O_2$ $[M+H]^+$ 333.2464 Found 333.2525.

2-phenylquinazolin-4(3H)-one (4a) –
Solid, Yield = 84%, mp = 176-178 ^{0}C FT-IR (KBr) ν (cm^{-1}): 3425, 2943, 2354, 1637, 1123, 761, ^{1}H NMR (400 MHz, DMSO-d_6): 12.5 (br s, 1H), 8.20 (t, *J* = 8.4 Hz, 3H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.59-7.50 (m, 4H) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): 162.7, 152.7, 149.2, 135.0, 133.1, 131.8, 129.0, 128.2, 127.9, 127.0, 126.3, 121.4 ppm, HRMS (ESI) Calcd. for $C_{14}H_{10}N_2O$ $[M+H]^+$ 223.0793 Found 223.0864.

2-(3,4,5-trimethoxyphenyl)quinazolin-4(3H)-one (4b) –
Solid, Yield = 81%, mp = 182-184 ^{0}C FT-IR (KBr) ν (cm^{-1}): 3414, 2913, 2354, 1627, 1106, 779, Yield = 61%, ^{1}H NMR (400 MHz, DMSO-d_6): 8.58 (d, *J* = 8.4 Hz, 1H), 8.37 (br s, 1H) 7.64-7.62 (m, 2H), 7.26-7.22 (m, 1H), 7.16 (s, 2H), 3.95 (s, 6H), 3.93 (s, 3H) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): 165.3, 153.7, 142.1, 140.9, 134.5, 132.2, 129.2, 124.4, 121.1, 116.7, 104.7, 102.3, 61.1, 56.5 ppm, HRMS (ESI) Calcd. for $C_{17}H_{16}N_2O_4$ $[M+H]^+$ 313.1110 Found 313.1185.

2-(4-methoxyphenyl)quinazolin-4(3H)-one (4c) –
Solid, Yield = 74%, mp = 173-175 ^{0}C FT-IR (KBr) ν (cm^{-1}): 3315, 2933, 2324, 1604, 1026, 761, ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.4 (brs, 1H), 8.21-8.13 (m, 3H), 7.84 (t, *J*=8.4 Hz, 1H), 7.72 (d, *J*=8.0 Hz, 1H), 7.51 (t, *J*=8.0 Hz, 1H), 7.10 (d, *J*=8.8 Hz, 2H), 3.88 (s, 3H) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.3, 161.8, 151.8, 148.9, 134.5, 129.4, 127.3, 126.1, 125.7, 124.7, 120.7, 113.9, 55.4 ppm, HRMS (ESI) Calcd. for $C_{15}H_{12}N_2O_2$ $[M+H]^+$ 253.0899 Found 253.0970.

2-(4-fluorophenyl)quinazolin-4(3H)-one (4d) –
Solid, Yield = 81%, mp = 165-167 ^{0}C FT-IR (KBr) ν (cm^{-1}): 3425, 2943, 2344, 1629, 1124, 789, ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.5 (br s, 1H), 8.31-8.24 (m, 2H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.86-7.22 (m, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 8.8 Hz, 2H) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): 122.6, 151.8, 149.1, 135.1, 130.9, 130.8, 129.7, 127.9, 127.0, 126.3, 121.3, 116.2, 115.9 ppm, HRMS (ESI) Calcd. for $C_{14}H_9FN_2O$ $[M+H]^+$ 241.6999 Found 241.0774.

Biological Materials and Methods:

In vitro HMG-CoA reductase inhibitory activity: The HMG-CoA reductase assay was performed using the HMG-CoA reductase assay kit from SigmaeAldrich. HMG-CoA (substrate), NADPH, assay buffer and enzyme HMGR were supplied with the assay kit.

Cell culture and adipogenic differentiation:

3T3-L1 mouse embryo fibroblasts cell line was obtained from the American Type Culture Collection. Cells were cultured in a humidified atmosphere at 37ºC and 5% CO_2 in Dulbecco's modified Eagle's medium (DMEM) containing 10% (v/v) heat-inactivated fetal bovine serum and antibiotic penicillin and streptomycin. For adipogenesis induction 50000 cells were seed in 24 multi-well plates. After 2 days of when cells achieved near complete confluence, culture media was replaced with adipogenesis media I (containing Insulin 5 µg/ml, IBMX 0.5 mM and Dexamethasone 250 nm in culture medium). This media was then replaced after 72 hours with adipogenesis media II (Insulin 5 µg/ml in DMEM with 10% FBS).After replacement of this media, cells were then maintained next 2 days in 10% FBS containing DMEM medium. Lipid globules in the adipogenic cells starts forming from day 4th onwards after treatment,

and fully developed adipocytes were observed after day 6-8th of adipogenesis treatment. More than 90% cells do have lipid globules at this stage.

Triglyceride assay and Oil Red O staining:

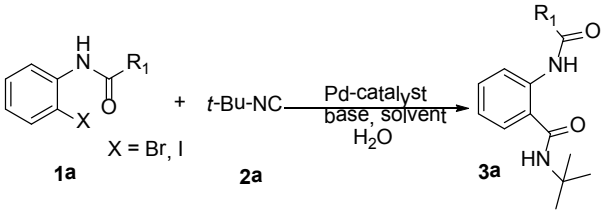
To study effect of compound on adipogenic differentiation, cells were differentiated as mentioned in above protocol along-with compound at stated concentrations. Fully differentiated 3T3-L1 (with or without compound) adipocytes were rinsed in phosphate buffered saline (pH 7.4). The adipocytes lipid globules were stained with Oil Red O (0.36% in 60% Isopropanol) for 20 min. Unstained Oil Red O was removed by rinsing wells twice with phosphate buffer saline. After complete removal of PBS, finally, 100% Isopropanol was used to extract the dye from the cells and extracted dye absorbance was measured at 492 nm.

Results and discussion

Chemistry

Based on our research interest in palladium catalysis, we found a few reported examples concerning palladium-catalyzed aminocarbonylation for the synthesis of amides from aryl halides.[27] However; the use of toxic carbon monoxide limited the scope of this kind of reaction.we initiated the study by using amide **1a** and *tert*-butyl isocyanide **2a** as a model substrates for the optimization of palladium-catalyzed tandem C-C/C-N coupling reaction. The investigation was carried out using different catalysts, base and solvents (Table 1). The reaction failed to proceed when palladium was expelled from the reaction (Table 1, entry 1). Among the three Pd-catalysts used ($PdCl_2$, $Pd(PPh)_3$ and $Pd(OAc)_2$), $Pd(OAc)_2$ was found to be the best and provided the product 3a in 89% yield in DMF as a solvent at 120 °C (Table 1, entry 4). Furthermore, $PdCl_2$ and $Pd(PPh)_3$ furnished the inferior yields of product 3a (Table 1, entry 2 and 3). We next tested the coupling reaction using various bases such as Cs_2CO_3, K_2CO_3, Na_2CO_3, K_3PO_4 and KO^{t}Bu in DMF at 120 °C, with $Pd(OAc)_2$ as a catalyst, among these bases Cs_2CO_3 was found to be the most effective base (Table 1, entry 4). Using $Pd(OAc)_2$ as catalyst and Cs_2CO_3 as base in DMSO provided slightly poor yield of 3a (Table 1, entry 9), while using toluene and CH_3CN under the same conditions furnished 3a in only poor yields (Table1, entry 10 and 11). The procedure was unfavourable when base was omitted from the reaction (Table 1, entry 12). Further optimization revealed that PPh_3 was essential in this reaction as well. Without PPh_3, the yield decreased to 71%.We next tested the aminocarbonylation reaction in the presence of different solvents. DMF/ H_2O (10:1) was superior to any other solvents The efficacy of tandem C-C/C-N cyclization reaction was affected when loading of the catalyst was reduced from 10 mol % to 5 mol % (Table 1, entry 13). It is interesting to note that the reaction was completed within 15-20 min under MW conditions at 120 °C, while in the absence of MW irradiations it took 4-5 h to reach the completion.

Table 1. Investigation of the Reaction Conditions for Pd-Catalyzed Coupling Reaction [a]



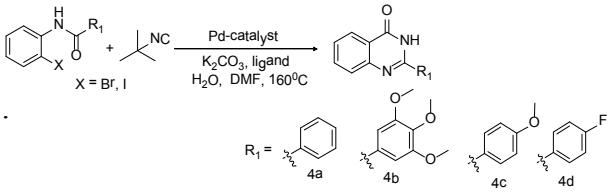
Entry	catalyst	base	solvent	yield % [b]
1	-	Cs_2CO_3	DMF	0[c]
2	$PdCl_2$	Cs_2CO_3	DMF	57

3	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	62
4	**$Pd(OAc)_2$**	**Cs_2CO_3**	**DMF**	**89**
5	$Pd(OAc)_2$	K_2CO_3	DMF	59
6	$Pd(OAc)_2$	K_3PO_4	DMF	41
7	$Pd(OAc)_2$	KO^t*Bu*	DMF	32
8	$Pd(OAc)_2$	Na_2CO_3	DMF	53
9	$Pd(OAc)_2$	Cs_2CO_3	DMSO	74
10	$Pd(OAc)_2$	Cs_2CO_3	Toluene	57
11	$Pd(OAc)_2$	Cs_2CO_3	CH_3CN	52
12	$Pd(OAc)_2$	-	DMF	0[d]
13	$Pd(OAc)_2$	Cs_2CO_3	DMF	39[e]

[a]Reaction conditions: substrate **1a** (1 mmol), *tert*-butyl isocyanide **2a** (1.2 mmol), catalyst (10 mol %), base (2 mmol), solvent (2 mL), reaction temperature (120 ^oC), reaction time (15 min), [b]isolated yield, [c]no addition of catalyst, [d] no addition of base, [e] loading of catalyst (5 mol %).

Scope of the strategy:

With acceptable conditions in hand (Table 1, entry 4), we extended it to the synthesis of various substituted N-Acyl Anthranilamide (**3a-n)** via amide precursors **(1a-n)** in moderate to good yields .



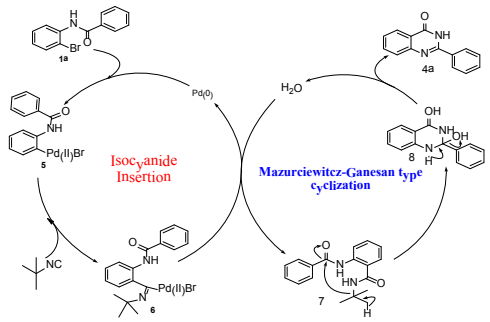
Scheme 2. Direct efficient cyclodehydration of N-acyl anthranilamides to quinazolinone respectively.

Literature methods are available for the efficient cyclodehydration of N-acyl anthranilamides to quinazolinone, respectively. However, we postulated that by conducting the Pd-catalyzed reaction at high temperature, both the isocyanide coupling and cyclization might be accomplished in a single step. Indeed, heating amides 2a with *tert*-butyl isocyanide at 160 ^0C in the With acceptable conditions directly provided the corresponding quinazolin-4-ones (4a- 4d) in good yields.

When monitored by 1H NMR, the initial N-acyl anthranilamideproduct (3a) are formed along with the heterocycles (4a) at early conversion. Notably, heating the isolated amide 3a in the absence of $Pd(OAc)_2$ resulted in negligible conversion to 4a, suggesting that cyclodehydration of 3a to 4a is facilitated by the Pd- catalyzed rather than being solely thermally induced. Although the reaction did not proceed at 120 ^oC temperature, good yields were obtained at 160 ^0C.

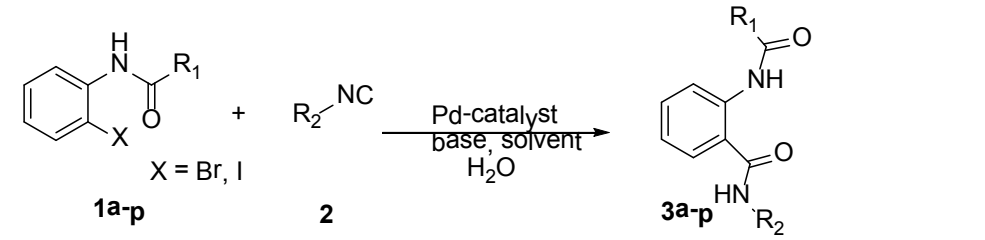
Reaction mechanism

A plausible mechanism for the synthesis of quinazolin-4-one of type **4a** is depicted in scheme 3. Thus, oxidative insertion of Pd to the amide precursor **1a** leads to the intermediate **5** which on insertion of *t*-butyl isocyanide leads to Pd(II) species **6**. Intermediate **6** via intramolecular cyclization followed by subsequent reductive elimination provides species **7**. Intermediate **7** then undergo Mazurciewitcz-Ganesan type[28] with de *tert*-butylation to afford **4a**.

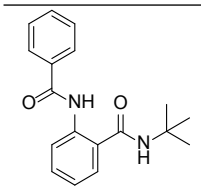


Scheme 3. Pd- catalyzed cascade reaction.

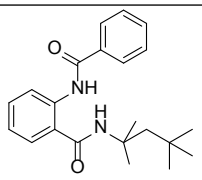
Figure 3. Synthesis of substituted N-acyl anthranilamide *via* a Pd-catalyzed coupling reaction of amide **1a-n** and different isocyanide **2**.



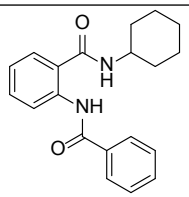
1a-p **2** **3a-p**



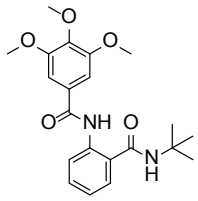
3a 76 %



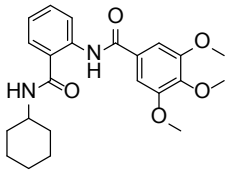
3b 71%



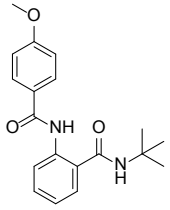
3c 83%



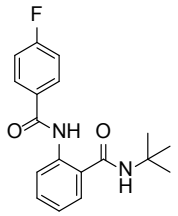
3d 78%



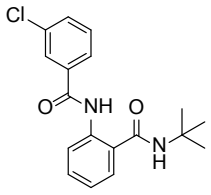
3e 75%



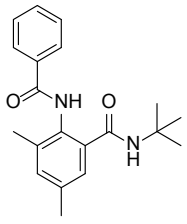
3f 83%



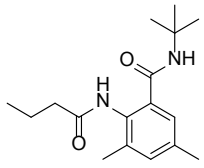
3g 76%



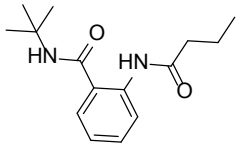
3h 82%



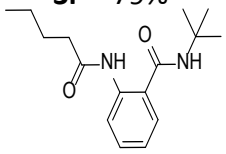
3i 79%



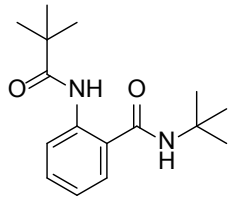
3j 77%



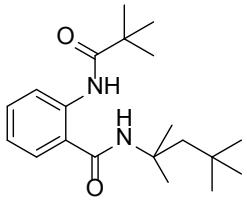
3k 81%



3l 78%



3m 85%



3n 79%

[a]Reaction conditions: $Pd(OAc)_2$ (10 mol %), Cs_2CO_3 (2 mmol), DMF (2 mL), MW, 120 °C, reaction time 20 min. Yields refer to isolated products.

Effects of compound on HMG-CoA reductase inhibition and Binding site analysis via docking –

Mevalonic acid (3,5-dihydroxy-3-methylpentanoic acid) is the unique precursor for mammalian sterol synthesis. Its synthesis is catalyzed by a two-step reductive deacylation of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) with the enzyme HMG-CoA reductase . Modulation of the functional level of HMG-CoA reductase is but one target in a complex regulatory strategy used to achieve cellular and whole body cholesterol homeostasis. Currently, the most common method of treating hypercholesterolemia is the use of HMG-CoA reductase inhibitors, also known as statins. These drugs block the rate-limiting step of cholesterol biosynthesis, ultimately resulting in up-regulation of the LDL-receptor and the clearing of low density lipoprotein (LDL) particles from the bloodstream.[29] As a class, statins have proven remarkably safe and effective for both primary prevention of coronary heart disease and secondary prevention of coronary events.[30] To meet the challenge of finding novel HMG-CoA reductase inhibitors with the efficacy and tolerability profiles needed to help patients achieve aggressive LDL reduction goals, we undertook a discovery effort to identify a novel class of inhibitors.

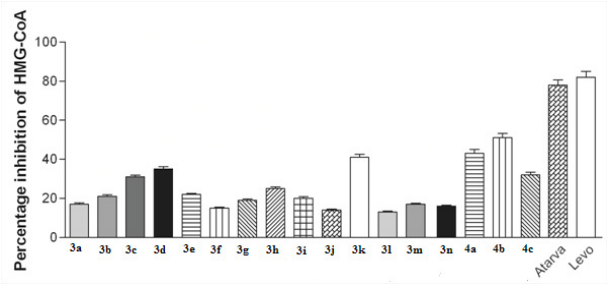


Figure.3 Percentage (%) inhibition of HMG-CoA reductase by lactams.

The inhibitory activity was evaluated at 100 µM (Fig. 3). Compound 3d, 3k, 4a and 4b were showing inhibition of HMG-CoA reductase at 100 µM concentration. Compound 4b was most active. After that we investigated the binding affinity of compounds towards the HMG-CoA reductase via molecular docking experiment.

Docking protocol

Autodok 4.2[31] has been used for molecular docking studies on four compounds **4b, 3d** and **3k** respectively with HMG-CoA reductase by treating the ligand as conformationally flexible. Reference protein coordinates for docking were obtained from the X-ray structure of catalytic portion of human HMG-CoA reductase (HMGR) complexed with simvastatin (PDB id: 1HW9). First, water molecules of the receptor molecule were removed and hydrogens were added. A binding pocket of the receptor was selected as the 6.5 Å around the bound simvastatin for the study. Grid maps for each atom type in the ligand were generated by using the Autogrid utility in Autodok 4.2. The following specifications were used for the grids. Grid with three coordinates (X=30 Å ,Y=34 Å,Z= 34 Å) with grid spacing set to 0.375 Å , was centred on the active site the centre having X, Y, and Z coordinates fixed at 3.928,-9.204 and -11.326 respectively. Docking was carried out with 20 GA runs, initial population size of 150 and 250000 maximum number of energy evaluations and 27000 maximum numbers of generations. Other docking parameters were set to default. Twenty conformations were generated for each ligand using Autodok 4.2. Docking simulations were performed using Autodok 4.2, implementing Lamarckian Genetic Algorithm (LGA). The interaction energies between the ligands and the HMG-CoA reductase calculated. The different docked conformations were ranked on the basis of their binding and docking energy scores and further analyzed for the possible interactions with the Protein. Molecular graphics images were produced using the PyMOL[32].

Finally the docked ligand-receptor complexes were selected according to the criteria of interacting energies combined with the geometrical matching quality. These complexes were used to have a comparative account of activity and their structural conformations. The total binding and docking energies between the compound and receptor was calculated according to the algorithm in the Autodok 4.2 programs. We found acceptable docking statistics with the HMG-CoA reductase.

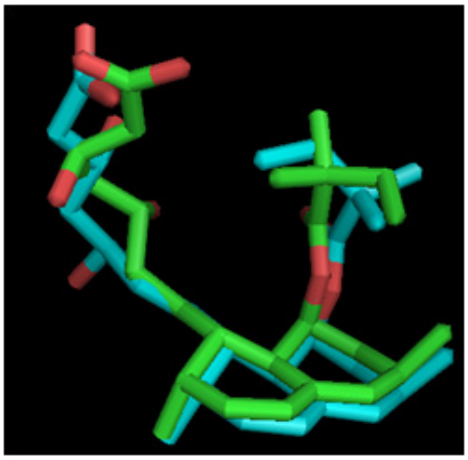


Figure 4. Conformation of crystallographic simvastatin (Cyan) as compared to the docked conformation (Green).

Molecular docking Analysis

To ensure that the ligand orientation and position obtained from the docking studies were likely to represent valid and reasonable binding modes of the inhibitors, the Autodok 4.2 program was first validated for the crystal structure used (1HW9). The ligand simvastatin was extracted and docked back to the corresponding binding pocket, to determine the ability of Autodok 4.2 to reproduce the position orientation of the ligand observed in the crystal structure. It was observed that Autodok 4.2 generated the optimal orientation of the docked simvastatin, close to that of the original orientation(figure 5) found in the crystal Molecular docking study was performed using Autodok 4.2 from Reference protein coordinates for docking were obtained from the X-ray structure of catalytic portion of human HMG-CoA reductase complexed with simvastatin (PDB ID: 1HW9).

Top-ranked ligands were analyzed for protein ligand interaction studies based on the Comparison of the hydrogen bond interaction among the top ranked docked poses with the protein and secondly, the analysis of binding and docking energies between the docked ligand and enzyme. Analysis of docking studies on three compounds of N-Acyl Anthranilamide and quinazolin-4-one derivatives (**3d**, **3k** and **4b**) showed that all these molecules fit well in the active site of HMG-CoA reductase (figure 5). These methoxy oxygen atoms of ligands 3d and 4b are interacting nitrogen atom of residue Lys735 through hydrogen bonding similarly as in the binding mode of simvastatin which give these ligands a fixed shape in the active site. The active site common residues were found to be Lys735, Ala751, Ala754, Glu559, Leu853, Ala856, Asn755, Leu562 and His752. These residues also show close hydrophobic contact with the ligands which gives further support to this mode of interaction of the ligand-substrate. The comparison of binding and docking energies also suggests that compound ligand **4b** has clearly edge over ligand **3d** and **3k** in the binding mode.

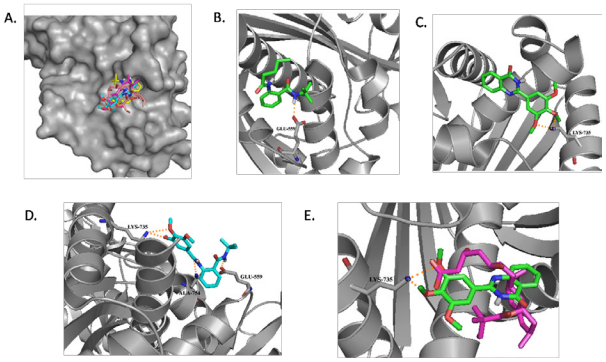


Figure 5. Ligand 3k (B), 4b (C), and 3d (D) ((green) and simvastatin(purple) are

in the binding site of HMG-CoA reductase (PDB ID: 1hw9. The protein molecule is shown in the ribbon representation, whereas docked compounds are illustrated in the stick representation. Hydrogen bonds are shown as orange dashed lines for ligands.

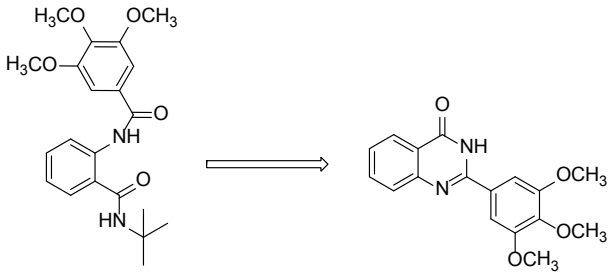


Figure 6. quinazolin-4-one derivatives are more potent than their corresponding N-Acyl Anthranilamide.

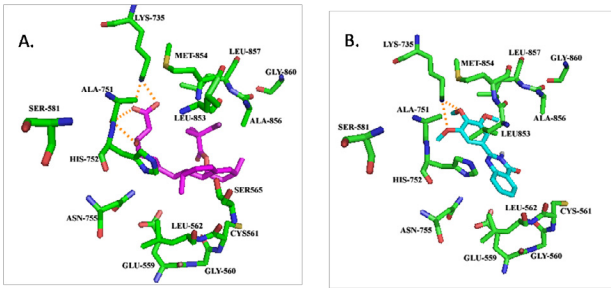


Figure 7. A. Docking of ligand 4b into the active site of HMG-CoA reductase (PDB ID: 1hw9). B. Docking of simvastatin into the active site of HMG-CoA reductase (PDB ID: 1hw9).

Adipogenesis is the process by which undifferentiated fibroblasts undergo morphological changes and accumulate lipid droplets as they become mature adipocytes.1 In an effort to control adipose levels in vivo for the treatment of obesity and diabetes, researchers have identified several genes that regulate adipogenesis. [33,34] The 3T3-L1 cell line has been particularly valuable in studying the molecular mechanisms underlying adipogenesis, owing to the difficulty of isolating primary preadipocytes from adipose tissue. The conversion of 3T3-L1 cells into adipocytes occurs through the temporal expression of genes over 6-8 days and can be initiated in vitro by the addition of a hormone cocktail consisting of dexamethasone, 3-isobutyl-1- methylxanthine, and insulin (commonly referred to as DMI).1 Importantly, transcription factors such as the nuclear receptors peroxisome proliferator-activated receptor-γ (PPARγ) and COUP transcription factor 2 (COUP-TFII) have been shown to regulate both the differentiation of 3T3-L1 cells in vitro and the development of adipose tissue in vivo, establishing the relevance of this cell-line model in the discovery of physiologically relevant adipogenesis pathways. Compound 4b was showing inhibition of adipogenesis at 10 µM concentration.

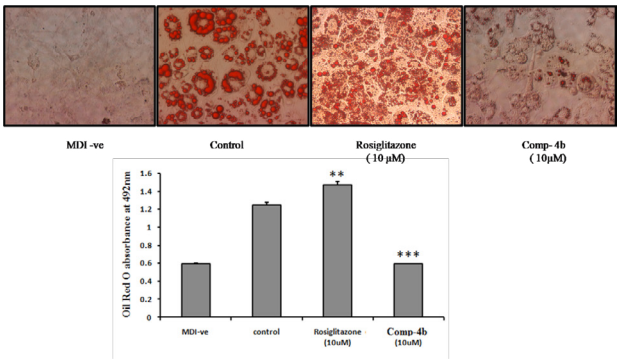


Figure 8. Effect of compound 4b on adipogenesis in 3T3-L1 cells.

Conclusion -

In summary, we have demonstrated a simple and highly efficient protocol for the synthesis of N-acyl anthranilamide and quinazolin-4-one derivatives via palladium-catalyzed C-C coupling of aryl amide with isocyanides for the first time, which is clearly different from the conventional procedures. The reactions are operationally simple and avoid using toxic carbon monoxide and acid chloride, which must be used in an anhydrous system. Most importantly, this transformation may be used

to discover new nature products and significant pharmaceuticals. We also demonstrated the biological potential of these compounds as novel HMG-CoA reductase inhibitor. Studies aimed at developing related transformations are underway.

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