How to Cite:
Lawaniya, Y. K., & Goyal, P. K. (2022). Synthesis of Novel Quinazolin-4-one hybrids as potential antimicrobial agents. *International Journal of Health Sciences*, *6*(S2), 6042–6054. https://doi.org/10.53730/ijhs.v6nS2.6573

Synthesis of Novel Quinazolin-4-one hybrids as potential antimicrobial agents

Yogesh Kumar Lawaniya
Bhupal Noble's Institute of Pharmaceutical Sciences, Bhupal Nobles', University, Udaipur -313001, India
Corresponding author email: yogeshlawaniya1984@gmail.com

Pradeep Kumar Goyal
Bhupal Noble's Institute of Pharmaceutical Sciences, Bhupal Nobles', University, Udaipur -313001, India

***Abstract*---**We have developed an effortless and extremely efficient procedure for the synthesis of quinazolin-4-one derivatives *via* palladium-catalyzed C-Ccoupling of aryl amide with isocyanides. The reactions are operationally simple and avoid using toxic carbon monoxide and acid chloride, which must be used in an anhydrous system. The structure of the novel compounds was confirmed based on spectral data. We also demonstrated the biological potential of these compounds as novel Antifungal Activity. Based on the MIC results, the most active is 3g.

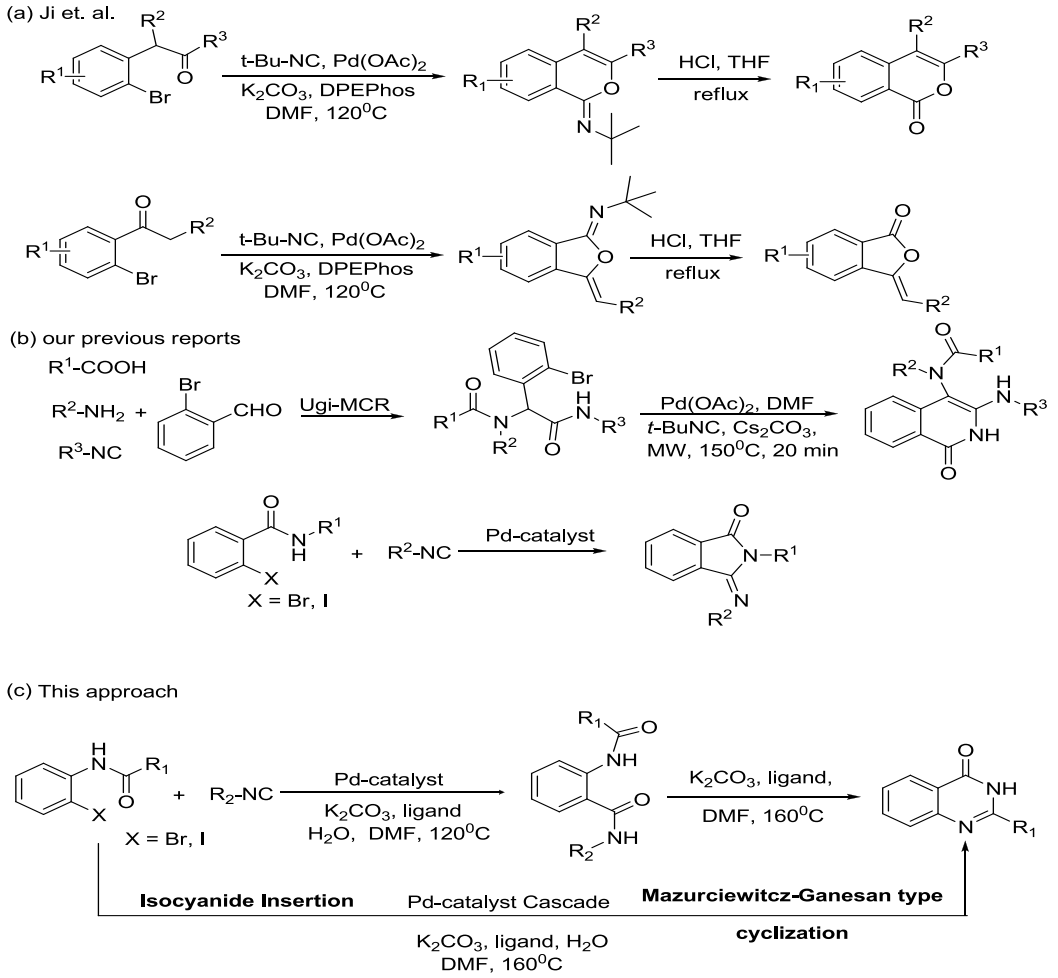
***Keywords*---**isoquinolines, N-acyl anthranilamides, potential antimicrobial.

Introduction

Over the last several decades, researchers have accomplished noteworthy progress in the field of organ metallic chemistry. The development of metal catalyzed cross-coupling reactions represents a paradigm shift in chemical synthesis, and today synthetic chemists can readily access carbon-carbon and carbon-heteroatom bonds from an enormous array 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 carbon-carbon and carbon-heteroatom bond formation have made a great contribution to the recent 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]

Recently, Ji et. al. reported a Pd-catalyzed synthesis of isocoumarins and phthalides via *tert*-butyl 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. Recent approaches using isocyanides as a coupling partner

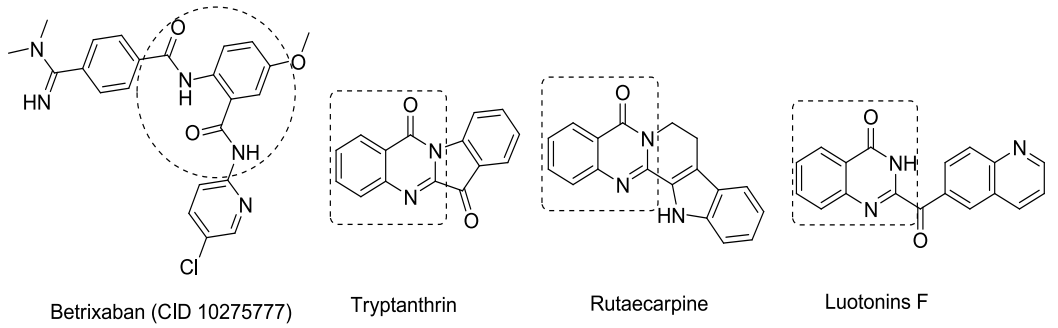


Figure 1. Some biologically active molecules and natural products containing N-Acyl anthranilamide, quinazolin-4-one motif

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]

Owing to the synthetic importance of 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 quinazolin-4-one derivatives in high yields using amide and isocyanides as coupling partner. Here we are also going to disclose the antimicrobial agent 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-h

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_20 (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 3a-h in 84-71% yields.

Characterization of compound

2-phenylquinazolin-4(3H)-one (3a)

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 (3b)

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 (3c)

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 (3d)

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.

2-(2-Chlorophenyl)-3*H*-quinazolin-4-one (3e)

This was obtained in 52% yield as white solid, mp. 188–190° C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.63 (brs, 1H), 8.17 (d, *J* = 7.1 Hz, 1H), 7.91 – 7.79 (m, 1H), 7.78 – 7.38 (m, 6H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 161.4, 152.2, 148.6, 134.6,

133.8, 131.6, 131.5, 130.8, 129.6, 127.4, 127.2, 127.0, 125.8, 121.2 ppm, HRMS (ESI) 257.00 $[M+H]^+$.

2-(4-Ethyl-phenyl)-3*H*-quinazolin-4-one (3f)

This was obtained in 79% yield as White solid mp 267-269 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.56 (s, br, 1H), 8.36 (d, J = 7.76 Hz, 1H), 8.20 (d, J =7.96 Hz, 2H), 7.80-7.86 (m, 2H), 7.50-7.54 (m, 1H), 7.43 (d, J=7.92, 2H), 2.78 (q, J = 7.52 Hz, 2H), 1.33 (t, J=7.56, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.77, 151.78, 149.65, 148.44, 134.82, 130.22, 128.60, 127.93, 127.38, 126.57, 126.38, 28.86, 15.30. MS (ESI) m/*z*: 251.14 $[M+H]^+$.

2-(4-Isopropyl-phenyl)-3*H*-quinazolin-4-one (3g)

This was obtained in 77% yield as White solid mp 233-235 ^{O}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.26 (s, br, 1H), 8.36 (d, J = 7.68 Hz, 1H), 8.16 (d, J =8.28 Hz, 2H), 7.86-7.80 (m, 2H), 7.54-7.50 (m, 1H), 7.41 (d, J=8.2, 2H), 2.74-2.70 (m, 1H), 1.78-1.70 (m, 3H), 1.02-0.99 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.54, 151.71, 149.62, 146.98, 134.84, 130.22, 129.25, 127.94, 127.18, 126.61, 126.40, 37.94, 24.31, 13.76. MS (ESI) m/*z*: 266.00 $[M+H]^+$.

2-(2-Chlorophenyl)-3*H*-quinazolin-4-one (3h)

This was obtained in 52% yield as white solid, mp. 188–190° C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.63 (brs, 1H), 8.17 (d, J = 7.1 Hz, 1H), 7.91 – 7.79 (m, 1H), 7.78 – 7.38 (m, 6H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 161.4, 152.2, 148.6, 134.6, 133.8, 131.6, 131.5, 130.8, 129.6, 127.4, 127.2, 127.0, 125.8, 121.2 ppm, HRMS (ESI) 257.00 $[M+H]^+$.

Materials and Methods

Fungus colonies were subcultured onto Sabouraud′s dextrose agar, SDA (Merck, Germany) and respectively incubated at 37 °C for 24 h and 25°C for 2-5 days. Suspensions of fungal spores were prepared in sterile PBS and adjusted to a concentration of 10^6cells/mL. Dipping a sterile swab into the fungal suspension and rolled on the surface of the agar medium. The plates were dried at room temperature for 15 min. Wells of 10 mm in diameter and about 7 mm apart were punctured in the culture media using sterile glass tube. 0.1 mL of several dilutions of fresh extracts was administered to fullness for each well. Plates were incubated at 37 °C. After incubation of 24 h bioactivities were determined by measuring the diameter of inhibition zone in mm. All experiments were made in triplicate and means were calculated.

Table 1: Proton and carbon chemical shift data of compound-3c

Carbon position	^{13}C Chemical shift (ppm)	^{1}H Chemical shift (ppm)
C-2	151.9	
3-N-H	-	12.40 (s)
C-4	162.3	-
C-4a	120.7	-

C-4b	148.9	-
C-5	125.7	8.13 (d, *J* = 7.85 Hz)
C-6	126.0	7.49 (t, *J* = 7.90 Hz)
C-7	134.4	7.81 (t, *J* = 7.90 Hz)
C-8	127.2	7.70 (d, *J* = 8.18 Hz)
C-1´	124.7	-
C-2´, C-6´	129.4	8.19 (d, *J* = 8.90 Hz)
C-3´, C-5´	113.9	7.08 (d, *J* = 8.90 Hz)
C-4´	161.8	-
C-4´-OCH_3	55.4	3.88 (s)

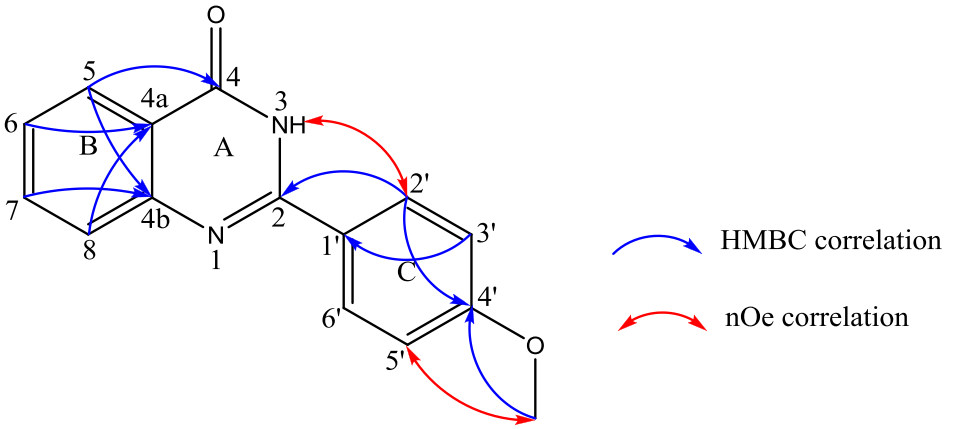


Figure 2: Important HMBC and nOe correlations

The complete ^{1}H and ^{13}C NMR signal assignments and connectivitywere determined from a combination of COSY, NOESY, HSQC, and HMBC data. COSY correlations established the two spin systems, which were H-5 to H-8 in ring-B and H-2´´,6´´ to H-3´´,5´´ in ring C. HMBC correlations of H-5 to C-4 and H-2´´,6´´ to C-2 showed that ring B and ring C are connected with ring A. An important nOe correlation between 3-N-H and H-2´determined the proximity of protons and strengthened the connectivity between ring A and ring C.

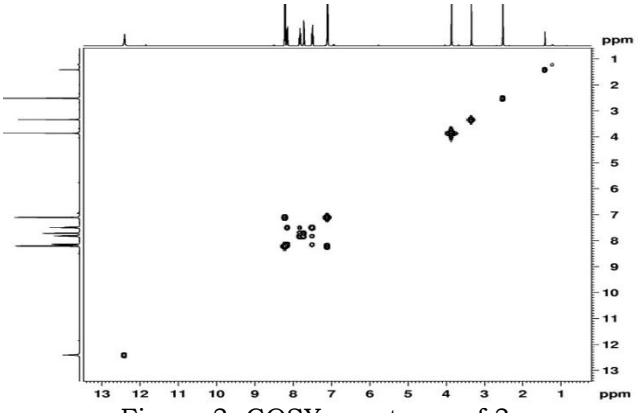


Figure 3: COSY spectrum of 3c

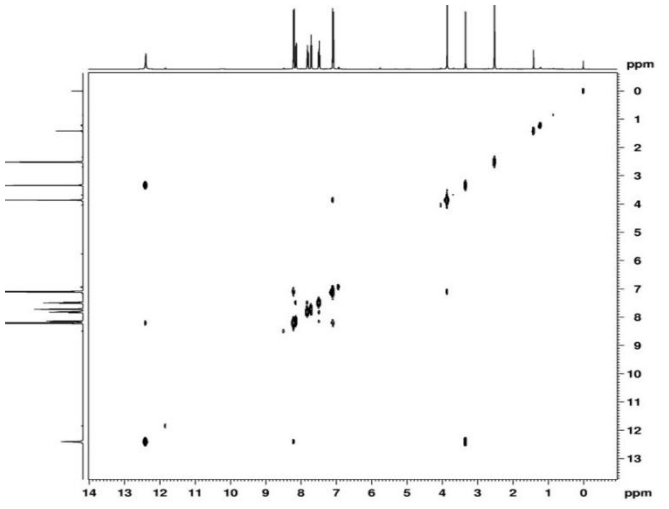


Figure 4: NOESY spectrum of 3c

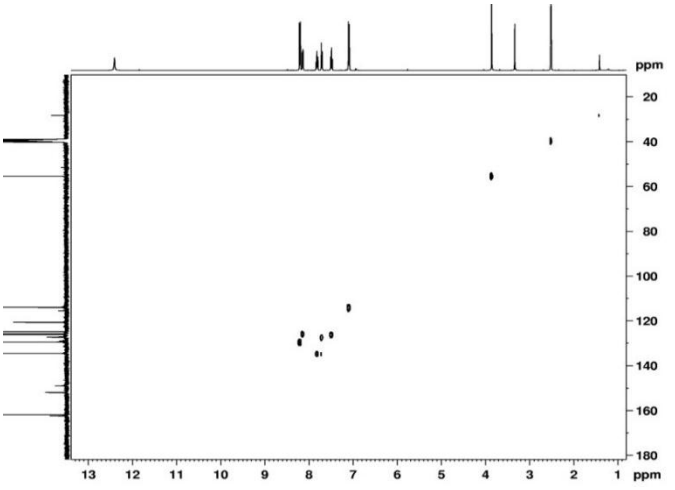


Figure 5: HSQC spectrum of 3c

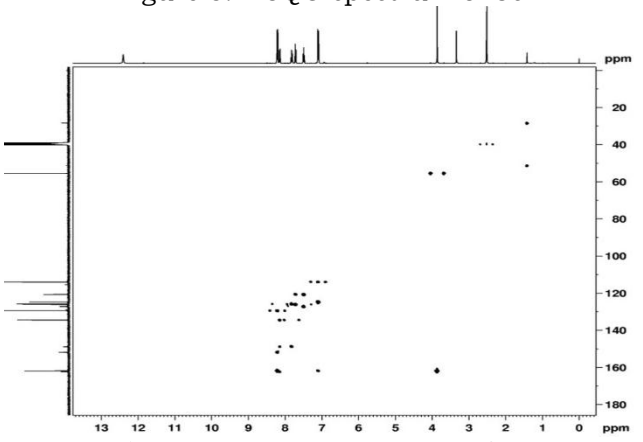
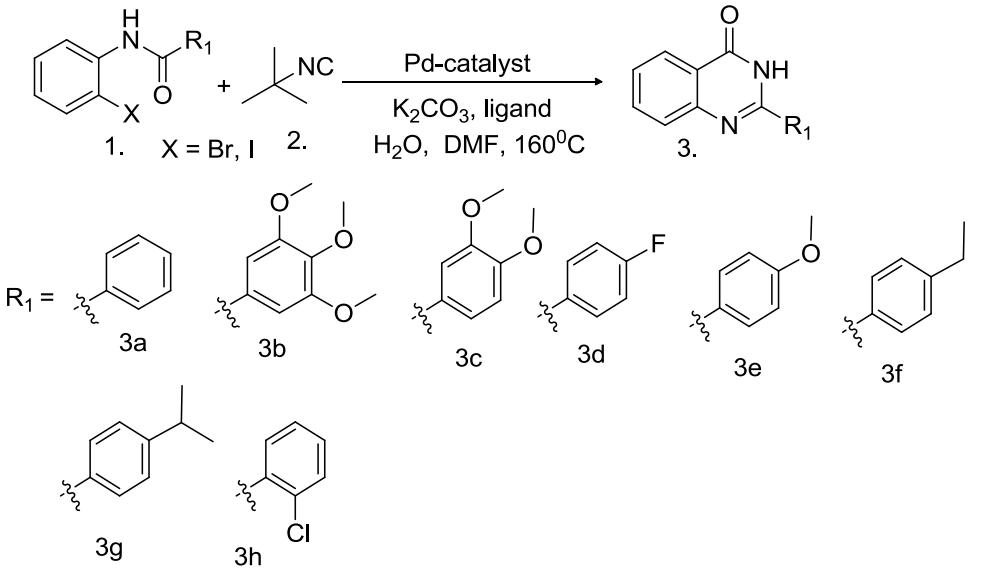


Figure 6: HMBC spectrum of 3c

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.



Scheme 1. 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 ^{0}C in with acceptable conditions directly provided the corresponding quinazolin-4-ones (3a- 3h) in good yields.

Table 2: Antifungal activity of quinazolinone derivatives (MIC in µg/ml)

Antifungal Activity MFC (µg/ml)			
Compound	*C. Albicans* MTCC 227	*A. Niger* MTCC 282	*A. Clavatus* MTCC 1323
3a	500	>1000	500
3b	>1000	250	500
3c	250	>1000	500
3d	1000	500	>1000

3e	1000	1000	>1000
3f	500	500	500
3g	250	250	>1000
3h	1000	500	500
Nystatin[b]	100	100	100
Greseofulvin[b]	500	100	100

[a]MIC = Minimum inhibitory concentration, the lowest concentration of the compound which inhibits the growth of the bacterium by at least 99%.
[b]Standard drug

From Table 2, the synthesized compounds showed significant activity against the tested fungal strains, i.e., 3c and 3g (MIC = 250 µg/mL) against *C. Albicans*. Equivalent inhibitory activity as compared to *Greseofulvin* was shown by compounds 3a and 3f having simple oxindole ring system (MIC = 500 µg/mL) against *C. Albicans*. Compound 3b and 6g having on quinazolinone ring system show significant activity (MIC = 250 µg/mL) against *A. Niger*. On the other hand, rest of the compounds showed poor MIC values compared to the reference compounds *Nystatin* and *Greseofulvin*.

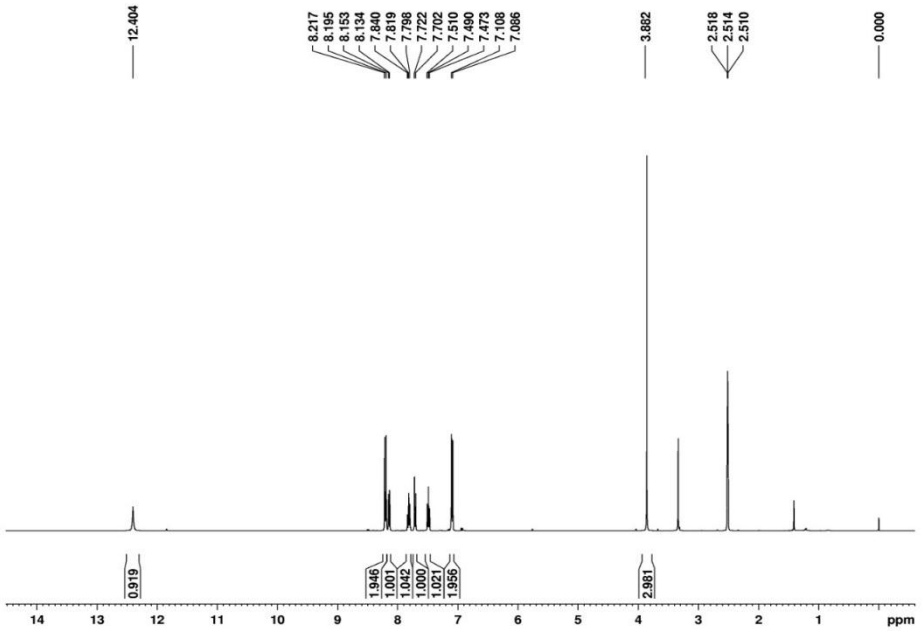


Figure 7: s: ^{1}H NMR spectrum of compound 3c

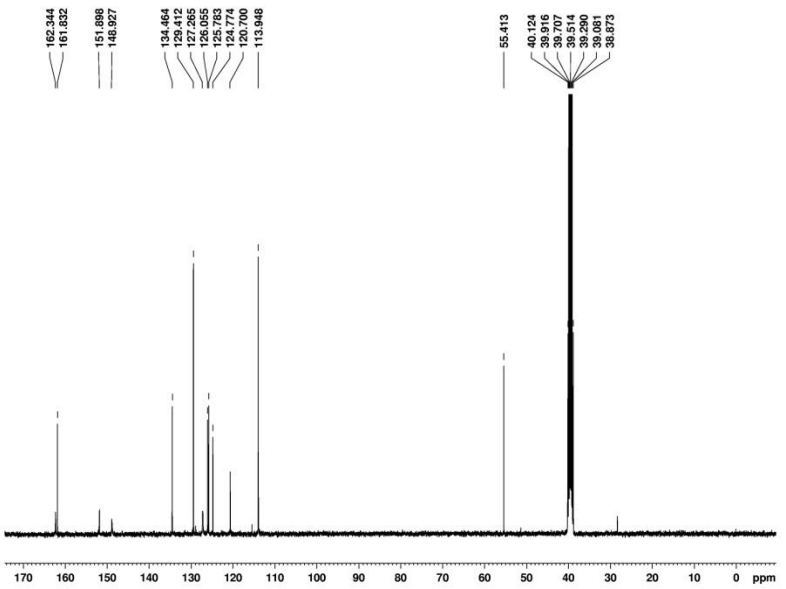


Figure 8: 2s. ^{13}CNMR spectrum of compound 3c

Conclusion

In summary, we have demonstrated a simple and highly efficient protocol for the synthesis of 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 Antifungal Activity. Studies aimed at developing related transformations are underway.

References

1. Wang, Y-F; Toh, K. K; Lee, J-Y.; Chiba, S. *Angew. Chem. Int. Ed.* 2011, *50*, 5927 (b) Tsukano, C.; Okuno, M.; Takemoto, Y. *Angew. Chem. Int. Ed.* 2012, *51*, 1 (c) Fusano, A.; Fukuyama, T.; Nishitani, S.; Inouye, T.; Ryu, I. *Org. Lett.* 2010, *12*, 2410, (d) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* 2009, *131*, 12050 (e) Okamoto, N.; Sakurai, K.; Ishikura, M.; Takeda, K.; Yanada, R. *Tetrahedron Lett.* 2009, *50*, 4167 (f) Nandi, S.; Samanta, S.; Jana, S.; Ray, J. K. *Tetrahedron Lett.* 2010, 51, 5294 (g) Ouyang, H. C.; Tang, R-Y.; Zhong, P.; Zhang, X-G.; Li, J-H. *J. Org. Chem.* 2011, *76*, 223 (h) Leibeling, M.; Pawliczek, M.; Kratzert, D.; Stalke, D.; Werz, D-B. *Org. Lett.* 2012, *14*, 346.
2. (a) Ma, B.; Wang, Y.; Peng, J.; Zhu, Q. *J. Org. Chem.* 2011, *76*, 6362 (b) Skoda-Foldes, R.; Kollar, L. *Curr. Org. Chem.* 2002, *6*, 1097 (c) Wu, X-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* 2010, *49*,

7316 (d) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J, G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K-I.; *Angew. Chem. Int. Ed.* 2009, *48*, 1830 (e) Giri, R.; Yu, J-Q, *J. Am. Chem. Soc*. 2008, *130*, 14082 (f) Yoo, E-J.; Wasa, M.; Yu, J-Q. *J. Am. Chem. Soc.* 2010, 132, 17378 (g) Fusano, A.; Fukuyama, T.; Nishitani, S.; Inouye, T.; Ryu, I. *Org. Lett.*, 2010, 12 2411 2410, (h) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* 2004, *69*, 6772 (i) Gimeno, A.; Medio-Simón, M.; Ramírez de Arellano, C.; Asensio, G.; Cuenca, A. B. *Org. Lett.* 2010, 12, 1900, (j) Saito, T.; Ogawa, S.; Takei, N.; Kutsumura, N.; Otani, T. *Org. Lett.,* 2011, *13*, 1098 (k) Yang, G.; Zhang, W. *Org. Lett.* 2012, 14, 268.

3. (a) Zhang, S.; Zhang, W.-X.; Xi, Z. *Chem. Eur. J.* 2010, 16, 8419 (b) Wang, Y.; Zhu, Q. *Adv. Synth. Catal.* 2012, *354*, 1902 (c) Van Baelen, G.; Kuijer, S.; Rýček, L.; Sergeyev, S.; Janssen, E.; De Kanter, F. J. J.; Maes, B. U. W.; Ruijter, E.; Orru, R. V. A. *Chem. Eur. J.* 2011, *17*, 15039 (d) Vlaar, T.; Ruijter, E.; Znabet, A.; Janssen, E.; De Kanter, F. J. J.; Maes, B. U. W.; Orru, R. V. A. *Org. Lett.* 2011, *13*, 6496 (e) Soeta, T.; Tamura, K.; Ukaji, Y. *Org. Lett.* 2012, *14*, 1226 (f) Liu, B.; Li, Y.; Jiang, H.; Yin, M.; Huang, H. *Adv. Synth. Catal.* 2012, *354*, 2288 (g) MacMillan, S. N.; Tanskia, J. M.; Waterman, R. *Chem. Commun.*, 2007, 4172 (h) Qiu, G.; He, Y.; Wu, J. *Chem. Commun.* 2012, *48*, 3836 (i) Masdeu, C.; Gómez, E.;. Williams, N. A. O.; Lavilla, R. *Angew. Chem. Int. Ed.* 2007, *46*, 3043.
4. Fei, X-D.; Ge, Z-Y.; Tang, T.; Zhu, Y-M.; Ji, S-J. *J. Org. Chem.,* 2013, *78*, 3170-5.
5. Tyagi, V.; Khan, S.; Giri, A.; Gauniyal, H. M.; Sridhar, B.; Chauhan, P. M. S. *Org. Lett.* 2012, *14*, 3126.
6. Tyagi, V; Khan, S; Chauhan, P.M. S, *Synlett,* 2013, *24*, 0645–0651.
7. Typing the name of these drug and drug candidates into PubChem provides the compound structure, bioactivity, full list of literature, and access to ongoing clinical trials, applications, and usage: betrixaban (CID 10275777) and tariquidar (CID 148201).
8. Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc*. 2010, *132*, 686.
9. Typing the name of these drugs into PubChem provides the compound structure, bioactivity, and access to ongoing clinical trials and applications: Tarceva (CID 176870) and Iressa (CID 123631).
10. Mhaske, S. B.; Argade, N. P. *Tetrahedron* 2006, *62*, 9787–9826.
11. Joseph P. M. *Nat. Prod. Rep*. 2003, *20*, 476–493.
12. (a) Bandekar, P. P.; Roopnarine, K. A.; Parekh, V. J.; Mitchell, T. R.; Novak, M. J.; Sinden, R. R. *J. Med. Chem.* 2010, *53*, 3558–3565. (b) Bhattacharjee, A. K.; Skanchy, D. J.; Jennings, B.; Hudson, T. H.; Brendle, J. J.; Werbovetz, K. A. *Bioorg. Med. Chem.* 2002, *10*, 1979–1989.
13. (a) Chen, A. L.; Chen, K. K. *J. Am. Pharm. Assoc*. 1933, *22*, 716. (b) Chiou, W.; Liao, J.; Chen, C. *J. Nat. Prod.* 1996, *59*, 374-378.
14. Liang, J. L.; Cha, H. C.; Jahng, Y. *Molecules* 2011, *16*, 4861-4883.
15. (a) Chinigo, G. M.; Paige, M.; Grindrod, S.; Hamel, E.; Dakshanamurthy, S.; Chruszcz, M.; Minor, W.; and Milton L. Brown *J. Med. Chem.* 2008, *51*, 4620–4631 (b) El-Azab, A. S.; ElTahir, K. E. H. *Bioorg. Med. Chem. Lett.* 2012, *22*, 1879–1885. (c) Saravanan, G.; Alagarsamy, V.; Prakash, C. R. *Bioorg. Med. Chem. Lett.* 2012, *22*, 3072–3078.
16. Wang, Z.; Wang, M.; Yao, X.; Li, Y.; Tan, J.; Wang, L.; Qiao, W.; Geng, Y.; Liu, Y.; Wang, Q. *Eur. J. Med. Chem.* 2012, *53*, 275-282.

17. (a) Abbas, S.; E.; Awadallah, F.; M.; Ibrahin, N.; A.; Said, E.; G.; Kamel, G.; M. *Eur. J. Med. Chem.* 2012, *53*, 141-149 (b) Amin, K. M.; Kamel, M. M.; Anwar, M. M.; Khedr, M.; Syam, Y. M. *Eur. J. Med. Chem.* 2010, *45*, 2117–2131.
18. (a) Al-Omary, F. A. M.; Abou-zeid, L. A.; Nagi, M. N.; Habib, E. E.; Abdel-Aziz, A. M.; El-Azab, A. S.; Abdel-Hamide, S. G.; Al-Omar, M. A.; Al-Obaid, A. M.; El-Subbagh, H. I. *Bioorg. Med. Chem. Lett.* 2010, *18*, 2849–2863 (b) Suresha, G.; P.; Suhas, R.; Kapfo, W.; Gowda, D. C. *Eur. J. Med. Chem.* 2011, *46*, 2530-2540.
19. Mohameda, M.; S.; Kamel, M.; M.; Kassem, E.; M.; M.; Abotaleb, N.; Abd El-moez, S.; I.; Ahmeda, M.; F. *Eur. J. Med. Chem.* 2010, *45*, 3311-3319.
20. Rudolph, J.; Esler, W.; P.; O'Connor, S.; Coish, P.; D.; G.; Wickens, P.; L.; Brands, M.; Bierer, D.; E.; Bloomquist, B.; T.; Bondar, G.; Chen, L.; Chuang, C.; Claus, T.; H.; Fathi, Z.; Fu, W.; Khire, U.; R.; Kristie, J.; A.; Liu, X.; Lowe, D.; B.; McClure, A.; C.; Michels, M.; Ortiz, A.; A.; Ramsden, P.; D.; Schoenleber, R.; W.; Shelekhin, T.; E.; Vakalopoulos, A.; Wang, L.; Yi, L.; Gardell, S.; J.; Livingston, J.; N.; Sweet, L.; J.; Bullock, W.; H. *J. Med. Chem.* 2007, *50*, 5202-5216.
21. Rhee, H.; Yoo, J.; H.; Lee, E.; Kwon, Y.; J.; Seo, H.; Lee, Y.; Choo, H.; P. *Eur. J. Med. Chem.* 2011, *46*, 3900-3908.
22. Ismail, M.; A.; H.; Barker, S.; Abou El Ella, D.; A.; Abouzid, K.; A.; M.; Toubar, R.; A.; Todd, M.; H. *J. Med. Chem.* 2006, *49*, 1526-1535.
23. Sharma, M.; Pandey, S.; Chauhan, K.; Sharma, D.; Kumar, B.; Chauhan, P. M. S. *J. Org. Chem.* 2012, *77*, 929.
24. Goldstein, J. L.; Brown, M. S. Nature 1990, *343*, 425.
25. For selected reviews on palladium-catalyzed aminocarbonylation, see: (a) Schoenberg, A.; Heck, R. F. J. Org. Chem. 1974, 39, 3327. (b) Cao, H.; McNamee, L.; Alper, H. Org. Lett. 2008, 10, 5281. (c) Brennfuhrer, A.; Neumann, H.; Beller, M. Angew. Chem., Int. Ed. 2009, 48, 4114. (d) Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. Angew. Chem., Int. Ed. 2007, 46, 8460. (e) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. J. Org. Chem. 2006, 71, 5951. (f) Salvadori, J.; Balducci, E.; Zaza, S.; Petricci, E.; Taddei, M. J. Org. Chem. 2010, 75, 1841. (g) Martinelli, J.R.;Freckmann, D. M. M.; Buchwald, S. L. Org. Lett. 2006, 8, 4843. (h) Barnard, C. F. J. Organometallics 2008, 27, 5402. (i) Kumar, K.; Zapf, A.; Michalik, D.; Tillack, A.; Heinrich, T.; B€ottcher, H.; Arlt,M.; Beller, M. Org. Lett. 2004,6, 7.
26. Mazurkiewicz, R *Monatsh. Chem.* 1989, *120*, 973. (b) Snider, B.; Zeng, H. *Heterocycles* 2003, *61*, 173. (c) Wang, H.; Ganesan, A. *J. Org. Chem.* 1998, *63*, 2432.
27. (a) McKenney, J. M. *Clin. Cardiol. (Suppl. III).* 2003, *26*, 32–38. (b) Speidal, K. M.; Hilleman, D. E. *Expert Opin. Pharmacother.* 2006, *7*, 1291–1304.
28. (a) Shepard, J.; Cobbe, S. M.; Ford, I.; Isles, C. G.; Lorimer, A. R.; MacFarlane, P. W.; McKillop, J. H.; Pachard, C. J. *N. Engl. J. Med.* 1995, *333*, 1301–1307. (b) LaRosa, J. C.; He, J.; Vupputuri, S. *JAMA, J. Am. Med. Assoc.* 1999, *282*, 2340–2346.
29. Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S. and Olson, A. J. , *J. Computational Chemistry* 2009, 16: 2785-91

30. DeLano,W.L. (2002) The PyMol Molecular Graphics System DeLano Scientific, San Carlos, CA,USA.
31. Ntambi, J. M.; Young-Cheul, K. J. Nutr. 2000, *130*, 3122S.
32. Cheung, K. J.; Tzameli, I.; Pissios, P.; Rovira, I.; Gavrilova, O.; Ohtsubo, T.; Chen, Z.; Finkel, T.; Flier, J. S.; Friedman, J. M. Cell Metab. 2007, *5*, 115.
33. Christianson, J. L.; Nicoloro, S.; Straubhaar, J.; Czech, M. P. J. Biol. Chem. 2008, *283*, 2906.