Synthesis of Novel Poly-substituted Quinolin-7-ones *via* Friedländer Hetero-Annulation Reaction from Anthranilic Acid and Flavanone Derivatives

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ABSTRACT: *Novel poly-substituted quinolin-7-one derivatives have been synthesized using Friedländer hetero-annulation reaction from anthranilic acid and flavanone derivatives catalyzed by nano-zinc oxide. Using eco-friendly Nano-catalyst led to mild reaction conditions and increasing in converted yields. Heterogeneous media makes easy work-up and high isolated yields. The use of ethanol as a green and environmental solvent is the other advantage of this method. Our studies were shown that steric factors have been found to be important in the formation of the desired product. Good and excellent yield (50-97%) was obtained for corresponding compounds. Characterization of products was performed by FT-IR, ^{1}H- and ^{13}C-Nuclear Magnetic Resonance spectroscopies, and elemental analysis. The retention factor, R_f, and melting point for these desired products were determined.*

KEY WORDS: *Friedländer reaction, Quinoline, Anthranilic acid, Flavanone, Nano Zinc oxide.*

INTRODUCTION

Alkaloids are nitrogen-containing compounds that are used as narcotics, pharmaceuticals, and poisons [1]. This family of natural compounds is classified into three groups; typical alkaloids, biological amines, and steroidal alkaloids [2]. Quinolines are one of the typical alkaloids and show several biological and pharmaceutical activities. Anti-malarial, anti-bacterial, anti-inflammatory, anti-asthmatic, anti-hypertensive, and tyrosine kinase inhibiting factors are some of these properties [3]. Quinolone derivatives are secondary metabolites that are synthesized by biosynthetic and chemical methods [2]. The most important chemical methods are Skraup, Doebner-Von Miller, Pfitzinger, Conrad- Limpach, Combes and Friedländer hetero-annulation [4]. One of the easiest routes for the synthesis of poly-substituted quinolones is the Friedländer reaction. It is the condensation reaction of 2-aminoaryl ketones with carbonyl compounds containing reactive α-methylene group and then cyclodehydration [5]. A literature survey shows basic or acidic catalyst is necessary for the completion or increasing of rate [5-15]. Following two previous reports [16], we decided to synthesis of a new category of this family. A family of natural compounds that has a fascinating biological activity is flavanones. Among these biological activities can be mentioned as anti-mycobacterial, anti-microbial, anti-lung cancer, anti-fungal, anti-viral, and anti-inflammatory [17-26]. In this research, flavanone derivatives were chosen as carbonyl compounds containing reactive α-methylene group, and Friedländer reaction was utilized by reaction between these compounds, anthranilic acid. Nano zinc oxide was selected as a catalyst (Scheme 1). This catalyst is

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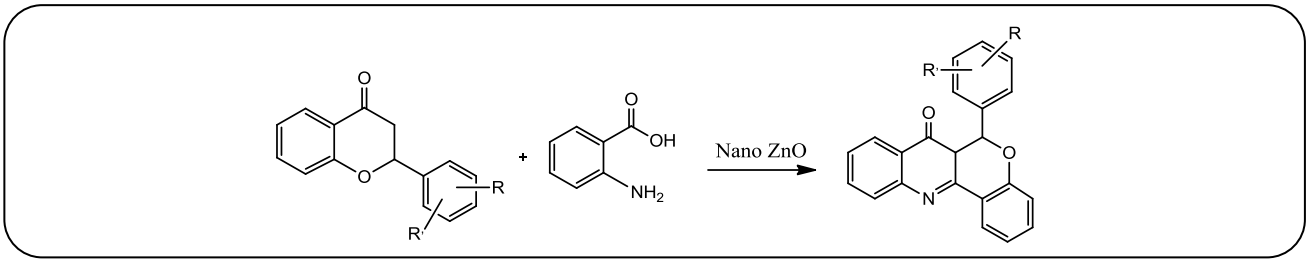


Scheme 1: Friedländer hetero-annulation reaction between flavanones and anthranilic acid.

an inexpensive, non-toxic, and eco-friendly heterogeneous catalyst that is used in the synthesis of coumarin derivatives [27], novel octahedron- quinolindiones [28], making antimicrobial textiles [29], as an antiwear additive in oil lubricants [30], and removal of nitrate ion from aqueous solutions [31].

Our studies showed that Nano zinc oxide acts as a heterogeneous catalyst in the synthesis of organic phosphorous compounds [32-33]. So, we decided to prepare novel quinoline derivatives by using this catalyst.

EXPERIMENTAL SECTION

The chemical materials were supplied from Merck Chemical Company. Nano zinc oxide (50 nm particle size and 97% purity) was bought from Sigma-Aldrich Company. NMR spectra were recorded on Ultra Shield Bruker 400, operating at 400 MHz (1H). Melting points were determined in open capillary tubes in a Büchi-545 circulating oil melting point. CHNS were recorded on a Vario EL automated analyzer, model 11086109". 1H-, 13C-NMR spectra and CHNS analysis data have been reported in the Supplemental Materials (Figures S1– S31).

General Procedure for the Synthesis of Poly-Substituted Quinolin-7-ones (2a-l)

We first synthesized appropriate flavanone (1 mmol) according to a previous report [33]. This flavanone was diluted and added to a mixture of anthranilic acid (1 mmol), nano zinc oxide (0.5mmol, 0.08 g), and ethanol (2 mL) within 5 min and was heated at 78°C for 24 h. Progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was centrifuged and decanted. The residue including the Nano catalyst was washed twice with distilled water and was dried in an oven at 100°C. The solution part was purified by silica gel column chromatography with *n*-hexane and ethyl acetate.

SUPPLEMENTARY MATERIALS AVAILABLE

Spectral data

6-Phenyl-6H-chromeno[4,3-b]quinolin-7(6aH)-one (2a): Yellow solid. FT-IR (KBr, cm^{-1}): 2925.1 (str. C-H), 1591.5 (C=O), 1561.5 (C=N), 1404.8 (C-O). ^{1}H-NMR (250 MHz, DMSO-d_6, δ/ppm): 2.86 (s, 1H, -CO-CH-), 5.64 (s, 1H, -CO-CH-), 6.43-6.64 (m, 2H, arom.), 7.06 (m, 2H, arom.), 7.39-7.54 (m, 5H, arom.), 7.73-7.76 (m, 4H, arom.). ^{13}C-NMR (100MHz, DMSO-d_6, δ/ppm): 55.6 (-CO-CH-), 79.0 (-CH-O-), 113.5, 115.9, 120.5, 123.1, 125.8, 126.7, 130.7, 132.7, 136.3, 139.3, 149.1, 150.5, 151.1, 163.4, 166.0, 168.0, 175.9 (C=N), 188.7 (C=O). Anal. Calc. for $C_{22}H_{15}NO_2$ (325.36): C, 81.21; H, 4.65; N, 4.30%. Found: C, 80.52; H, 4.60, 4.28%.

6-(4-Chlorophenyl)-6H-chromeno[4,3-b]quinolin-7(6aH)-one (2b)

White solid, FT-IR (KBr, cm^{-1}): 2921.2 (str. C-H), 1578.2 (C=O), 1561.6 (C=N), 1402.4 (C-O), 752.4 (C-Cl). ^{1}H-NMR (400MHz, DMSO-d_6, δ/ppm): 2.56 (s, 1H, -CO-CH), 5.17 (s, 1H, -CH-O-), 6.59-6.76 (m, 6H, arom.), 7.19-7.23 (m, 3H, arom.), 7.64-7.89 (m, 3H, arom.). ^{13}C-NMR (100MHz, DMSO-d_6, δ/ppm): 52.8 (-CO-CH-), 79.4 (-CH-O-), 113.8, 114.0, 11.4, 114.7, 115.0, 115.7, 129.0, 130.22, 130.23, 131.9, 132.1, 141.5, 141.8, 150.60, 150.66, 174.0, 174.3 (C=N), 187.9 (C=O). Anal. Calc. for $C_{22}H_{14}ClNO_2$ (359.81): C, 73.44; H, 3.92; N, 3.89%. Found: C, 72.51; H, 3.83, N, 3.83%.

4-(7-Oxo-6a,7-dihydro-6H-chromeno[4,3-b]quinolin-6-yl)benzonitrile (2c)

Yellow solid, FT-IR (KBr, cm^{-1}): 2934.5 (str. C-H), 1646.9 (C=O), 1512.1 (C=N), 1398.7 (C-O). ^{1}H-NMR (400MHz, DMSO-d_6, δ/ppm): 2.60 (s, 1H, -CO-CH), 5.67 (s, 1H, -CH-O-), 6.53-6.76 (m, 7H, arom.), 7.21 (m, 2H, arom.), 7.86-7.88 (m, 3H, arom.). ^{13}C-NMR (100MHz, DMSO-d_6, δ/ppm): 52.21 (-CO-CH-), 71.24 (-CH-O-),

112.7, 113.5, 114.4, 115.4, 116.4, 126.9, 127.3, 129.3, 131.6, 132.1, 133.5, 133.9, 138.1, 150.0, 150.3, 167.8, 174.0 (C=N), 192.9 (C=O). Anal. Calc. for $C_{23}H_{14}N_2O_2$ (350.37): C, 78.84; H, 4.03; N, 8.00%. Found: C, 77.81; H, 3.95; N, 7.63%.

6-(4-Bromophenyl)-6H-chromeno[4,3-b]quinolin-7(6aH)-one (2d)

Yellow solid, FT-IR (KBr, cm^{-1}): 2931.8 (str. C-H), 1588.2 (C=O), 1554.8 (C=N), 1411.5 (C-O), 754.7 (C-Br). ^{1}H-NMR (400MHz, DMSO-d_6, δ/ppm): 2.50 (s, 1H, -CO-CH), 5.68 (s, 1H, -CH-O-), 6.44-6.64 (m, 6H, arom.), 7.07-7.09 (m, 3H, arom.), 7.76-7.78 (m, 3H, arom.). ^{13}C-NMR (100MHz, DMSO-d_6, δ/ppm): 53.7 (-CO-CH-), 79.8 (-CH-O-), 111.5, 113.5, 114.1, 114.4, 118.4, 121.0, 123.7, 126.9, 127.9, 128.5, 129.6, 130.2, 131.3, 132.5, 150.0, 150.3, 174.1 (C=N), 191.2 (C=O). Anal. Calc. for $C_{22}H_{14}BrNO_2$ (404.26): C, 65.36; H, 3.49; N, 3.46%. Found: C, 65.51; H, 3.50; N, 3.40%.

6-(4-Fluorophenyl)-6H-chromeno[4,3-b]quinolin-7(6aH)-one (2e)

Yellow solid, FT-IR (KBr, cm^{-1}): 2924.5 (str. C-H), 1594.7 (C=O), 1551.6 (C=N), 1405.7 (C-O), 1067.5 (C-F). ^{1}H-NMR (400MHz, DMSO-d_6, δ/ppm): 2.62 (s, 1H, -CO-CH-), 5.47 (s, 1H, -CH-O-), 6.55-6.77 (m, 8H, arom.), 7.20-7.23 (m, 2H, arom.), 7.88-7.90 (m, 2H, arom.). ^{13}C-NMR (100MHz, DMSO-d_6, δ/ppm): 55.4 (-CO-CH-), 72.2 (-CH-O-), 110.7, 114.4, 114.7, 115.4, 116.1, 116.7, 123.6, 124.6, 127.6, 127.9, 130.5, 131.6, 131.9, 133.2, 150.0, 173.7, 174.4 (C=N), 191.9 (C=O). Anal. Calc. for $C_{22}H_{14}FNO_2$ (343.10): C, 76.96; H, 4.11; N, 4.08%. Found: C, 76.51; H, 4.10; N, 4.00%.

6-(4-Nitrophenyl)-6H-chromeno[4,3-b]quinolin-7(6aH)-one (2f)

Yellow solid, FT-IR (KBr, cm^{-1}): 2925.1 (str. C-H), 1598.2 (C=O), 1551.5 (C=N), 1408.1 (C-O), 1384.8 (N=O). ^{1}H-NMR (400MHz, DMSO-d_6, δ/ppm): 2.65 (s, 1H, -CO-CH-), 5.25 (s, 1H, -CH-O-), 6.54-6.76 (m, 6H, arom.), 7.21 (m, 2H, arom.), 7.87-7.89 (m, 4H, arom.). ^{13}C-NMR (100MHz, DMSO-d_6, δ/ppm): 55.4 (-CO-CH-), 76.5 (-CH-O-), 113.7, 114.4, 114.7, 116.4, 118.7, 119.0, 120.0, 120.6, 121.3, 121.7, 124.6, 129.6, 130.5, 132.2, 150.3, 174.0 (C=N), 191.2 (C=O). Anal. Calc. for $C_{22}H_{14}N_2O_4$ (370.36): C, 71.35; H, 3.81; N, 7.56%. Found: C, 70.61; H, 3.51; N, 7.80%.

6-(p-Tolyl)-6H-chromeno[4,3-b]quinolin-7(6aH)-one (2g)

Yellow solid, FT-IR (KBr, cm^{-1}): 2935.1 (str. C-H), 1591.5 (C=O), 1544.8 (C=N), 1404.8 (C-O). ^{1}H-NMR (400MHz, DMSO-d_6, δ/ppm): 2.45 (s, 3H, Ar-CH_3), 2.94 (d, *J*=4 Hz, 1H, -CO-CH-), 5.73 (d, *J*=4Hz, 1H, -CH-O-), 6.58-6.78 (m, 7H, arom.), 7.23 (m, 3H, arom.), 7.88-7.90 (m, 2H, arom.). ^{13}C-NMR (100MHz, DMSO-d_6, δ/ppm): 20.1 (Ar-CH_3), 53.4 (-CO-CH-), 78.6 (-CH-O), 110.8, 114.1, 115.7, 118.0, 121.3, 126.2, 126.6, 129.5, 132.0, 132.1, 135.8, 136.2, 137.8, 150.6, 174.0 (C=N), 191.2 (C=O). Anal. Calc. for $C_{22}H_{17}NO_2$ (339.39): C, 81.40; H, 5.05; N, 4.13%. Found: C, 81.32; H, 4.98; N, 4.08%.

6-(4-Methoxyphenyl)-6H-chromeno[4,3-b]quinolin-7(6aH)-one (2h)

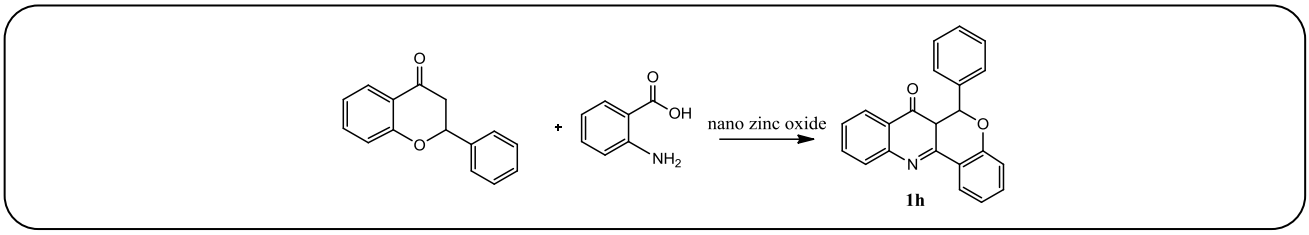
Yellow solid, FT-IR (KBr, cm^{-1}): 2931.8 (str. C-H), 1594.8 (C=O), 1544.8 (C=N), 1408.1 (C-O). ^{1}H-NMR (400MHz, DMSO-d_6, δ/ppm): 2.86 (d, J=4Hz, 1H, -CO-CH-), 3.88 (s, 3H, -OCH_3), 5.69 (d, *J*=4Hz, 1H, -CH-O-), 6.56-6.76 (m, 6H, arom.), 7.21 (m, 3H, arom.), 7.89-7.90 (m, 3H, arom.). ^{13}C-NMR (100MHz, DMSO-d_6, δ/ppm): 43.3 (-CO-CH-), 55.1 (-OCH_3), 78.5 (-CH-O), 113.8, 114.1, 115.7, 118.0, 121.3, 126.2, 128.2, 130.2, 130.5, 132.0, 132.1, 136.2, 150.6, 159.3, 161.1, 174.3 (C=N), 191.8 (C=O). Anal. Calc. for $C_{29}H_{23}NO_3$ (433.50): C, 80.33; H, 5.35; N, 3.23%. Found: C, 79.98; H, 5.30; N, 3.25%.

6-(3-Methoxyphenyl)-6H-chromeno[4,3-b]quinolin-7(6aH)-one (2i)

Yellow solid, FT-IR (KBr, cm^{-1}): 2925.1 (str. C-H), 1568.2 (C=O), 1548.2 (C=N), 1404.8 (C-O). ^{1}H-NMR (400MHz, DMSO-d_6, δ/ppm): 2.92 (d, *J*=16 Hz, 1H, -CO-CH-), 3.47 (s, 3H, -OCH_3), 5.74 (d, *J*=16 Hz, 1H, -CH-O-),6.71-6.75 (m, 7H, arom.), 7.20 (m, 3H, arom.), 7.87 (m, 2H, arom.). ^{13}C-NMR (100MHz, DMSO-d_6, δ/ppm): 43.5 (-CO-CH-), 54.4 (-OCH_3), 78.2 (-CH-O-), 111.8, 112.1, 113.5, 113.8, 114.4, 115.0, 116.1, 118.4, 118.7, 121.7, 126.3, 128.2, 130.2, 131.3, 132.8, 134.2, 136.5, 150.6, 173.4 (C=N), 192.6 (C=O). Anal. Calc. for $C_{23}H_{17}NO_3$ (355.39): C, 77.73; H, 4.82; N, 3.94%. Found: C, 77.51; H, 4.77; N, 4.00%.

6-(2-Hydroxyphenyl)-6H-chromeno[4,3-b]quinolin-7(6aH)-one (2j)

White solid, FT-IR (KBr, cm^{-1}): 3011.8 (O-H), 2921.8 (str. C-H), 1574.8 (C=O), 1551.5 (C=N), 1398.1 (C-O).



Scheme 2: Choice reaction to optimize of conditions.

^{1}H-NMR (400MHz, DMSO-d_6, δ/ppm): 2.54 (s, 1H, -CO-CH-), 5.22 (s, 1H, -CH-O-), 6.51-6.73 (m, 7H, arom.), 7.18 (m, 2H, arom.), 7.85-7.87 (m, 3H, arom.), 8.89 (s, broad peak, -OH). ^{13}C-NMR (100MHz, DMSO-d_6, δ/ppm): 51.7 (-CO-CH-), 74.2 (-CH-O), 113.8, 114.0, 115.4, 116.0, 116.4, 131.2, 131.8, 132.5, 133.5, 135.5, 136.2, 144.1, 148.3, 151.0, 153.9, 157.3, 164.2, 171.4, 174.0 (C=N), 189.2 (C=O). Anal. Calc. for $C_{22}H_{15}NO_3$ (341.36): C, 77.41; H, 4.43; N, 4.10%. Found: C, 77.31; H, 4.35; N, 3.98%.

6-(5-Bromo-2-hydroxyphenyl)-6H-chromeno[4,3-b]quinolin-7(6aH)-one (2k)

Light red solid, FT-IR (KBr, cm^{-1}): 3128.5 (O-H), 2925.1 (str. C-H), 1608.2 (C=O), 1464.8 (C=N), 1311.5 (C-O), 751.4 (C-Br). ^{1}H-NMR (400MHz, DMSO-d_6, δ/ppm): 2.62 (s, 1H, -CO-CH-), 4.50 (s, 1H, -CH-O-), 6.55-6.77 (m, 8H, arom.), 7.22-7.23 (m, 2H, arom.), 7.88-7.90 (m, 2H, arom.), 8.92 (s, broad peak, -OH). ^{13}C-NMR (100MHz, DMSO-d_6, δ/ppm): 55.4 (-CO-CH-), 73.9 (-CH-O), 111.5, 113.4, 114.4, 115.4, 115.7, 117.4, 117.7, 124.0, 125.3, 131.6, 132.1, 134.8, 141.4, 145.1, 145.7, 149.0, 150.3, 173.4, 173.7 (C=N), 191.5 (C=O). Anal. Calc. for $C_{22}H_{14}BrNO_3$ (420.26): C, 62.87; H, 3.36; N, 3.33%. Found: C, 62.51; H, 3.40; N, 3.38%.

6-(Naphthalen-2-yl)-6H-chromeno[4,3-b]quinolin-7(6aH)-one (2l)

Yellow solid, FT-IR (KBr, cm^{-1}): 2928.4 (str. C-H), 1588.2 (C=O), 1578.2 (C=N), 1401.5 (C-O). ^{1}H-NMR (400MHz, DMSO-d_6, δ/ppm): 2.63 (s, 1H, -CO-CH-), 5.19 (s, 1H, -CH-O-), 6.74-6.76 (m, 7H, arom.), 7.20-7.21 (m, 4H, arom.), 7.56-7.64 (m, 2H, arom.), 7.87-7.89 (m, 2H, arom.). ^{13}C-NMR (100MHz, DMSO-d_6, δ/ppm): 55.4 (-CO-CH-), 71.5 (-CH-O), 111.5, 111.8, 113.5, 114.0, 115.0, 115.7, 116.4, 120.6, 122.0, 123.7, 128.6, 128.9, 130.2, 130.5, 131.2, 132.5, 142.4, 148.3, 149.4, 150.0, 151.3, 155.6, 167.5, 174.0 (C=N), 192.5 (C=O). Anal. Calc. for $C_{26}H_{17}NO_2$ (375.42): C, 83.18; H, 4.56; N, 3.73%. Found: C, 83.23; H, 4.53; N, 3.84%.

RESULTS AND DISCUSSION

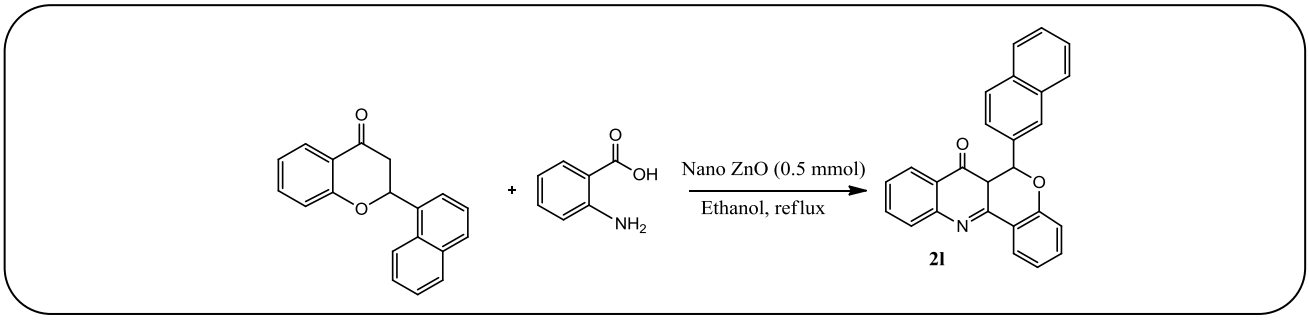
For the optimization of reaction, 2-phenylchroman-4-one (1h) was synthesized and chosen as the simplest flavanone (Scheme 2).

Solvent and temperature are two effective parameters in the progress of the reaction. The first factor that was investigated is the solvent's role. Different solvents were added to a mixture of 2-Phenylchroman-4-one (1 mmol), anthranilic acid (1 mmol), and nano zinc oxide (0.5 mmol, 0.08 g), and the reaction mixture was stirred at room temperature. These results were summarized in Table 1, Entries 1-5. The best result was obtained in ethanol (Entry 2). Raising temperature leads to increase yields (Table 1, Entries 6-10). Ethanol and dimethyl sulfoxide (DMSO) were the ideal solvents. We chose ethanol as the most suitable solvent because it is a green and eco-friendly solvent. The amounts of catalyst were studied in ethanol under reflux conditions (Table 1, Entries 11-13). The best conditions are summarized in Table 1, entry 7.

We can extend our procedure to the synthesis of the other quinoline-7-ones. Different flavanones react with anthranilic acid in the presence of a catalyst in ethanol under reflux conditions. Table 2 shows these results. Numerous flavanones (**1a-o**) with electron-withdrawing and electron releasing groups were examined. In most the cases, the reaction mixture was stirred overnight. The corresponding quinolines were synthesized in good to excellent yields (**2a-l**). 2-(4-Bromophenyl) chroman-4-one, **2d**, and 2-(4-fluorophenyl) chroman-4-one, **2e**, produce quinolone-7-ones in the highest yields. In place of electron-releasing groups, the isolated yields are decreasing (Table 2, Entries **2g-2l**). The reaction between 2-(naphthalen-2-yl)chroman-4-one and anthranilic acid, (Table 2, Entry 12), were shown in Scheme 3.

Table 1: Optimized Conditions for Model Reaction.

Entry	Solvent	Temp. (°C)	Catalyst (mmol)	Time (h)	Isolated Yields (%)
1	Solvent-free	r.t.	0.5	24	30
2	Ethanol	r.t.	0.5	24	89
3	DMF	r.t.	0.5	24	25
4	DMSO	r.t.	0.5	24	25
5	CH_2Cl_2	r.t.	0.5	24	trace
6	Solvent-free	reflux	0.5	24	55
7	Ethanol	reflux	0.5	24	95
8	DMF	reflux	0.5	24	75
9	DMSO	reflux	0.5	24	90
10	CH_2Cl_2	reflux	0.5	24	25
11	Ethanol	reflux	-	24	trace
12	Ethanol	reflux	0.25	24	83
13	Ethanol	reflux	0.75	24	95



Scheme 3: Synthesis of 6-(Naphthalen-2-yl)-6H-chromeno[4,3-b]quinolin-7(6aH)-one (2l).

2-(2-Chlorophenyl) chroman-4-one (**2m**), 2-(2-methoxyphenyl) chroman-4-one (**2n**) and 2-(2,4-dichlorophenyl) chroman-4-one (**2o**) don´t react even up to 48 hours. Probably, compared to the polar effect, the steric factor seems more important.

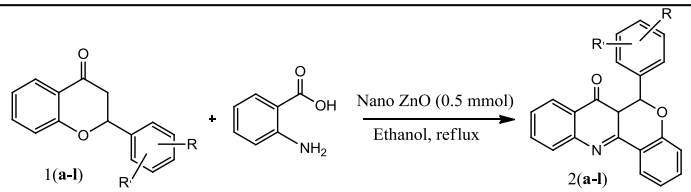
The probable mechanism suggested for this reaction (Scheme 4).

Nanocatalyst was centrifuged and isolated. The reaction between 2-phenylchroman-4-one (**1h**) and anthranilic acid was repeated four times. The results were shown that Nanocatalyst will be deactivated after use twice (Scheme 5).

CONCLUSIONS

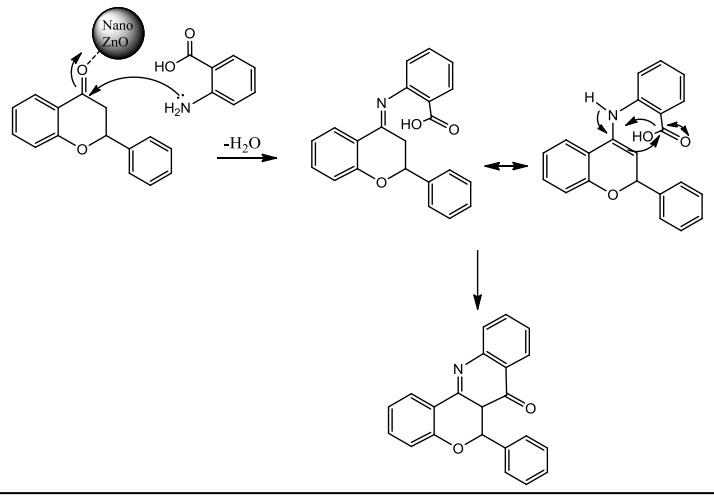
Novel derivatives of poly-substituted quinoline-7-ones have been prepared using Friedländer hetero-annulation reaction from anthranilic acid and flavanone derivatives catalyzed by nano-zinc oxide. This method is an appropriate way for this purpose because of its simplicity and use of heterogeneous and eco-friendly catalysts. Good

Table 2: Synthesis of quinolin-7-ones in the presence of Nano-ZnO.

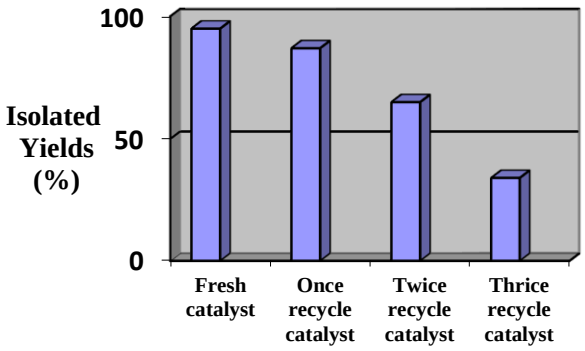


Entry	Products	R	R´	Time (h)	Isolated Yield (%)	m.p. (°C)	R_f[a]
1	2a	H	H	24	95	221	0.50
2	2b	H	4-Cl	24	96	229	0.42
3	2c	H	4-CN	24	90	314	0.75
4	2d	H	4-Br	24	98	267	0.50
5	2e	H	4-F	24	97	308	0.50
6	2f	H	4-NO_2	24	84	289	0.75
7	2g	H	4-CH_3	24	59	238	0.25
8	2h	H	4-OCH_3	24	73	241	0.25
9	2i	H	3-OCH_3	24	64	300	0.25
10	2j	H	2-OH	24	69	277	0.80
11	2k	5-Br	2-OH	24	50	251	0.50
12	2l	2- Naphthyl		24	58	227	0.28
13	2m	H	2-Cl	48	No reaction	-	-
14	2n	H	2-OCH_3	48	No reaction	-	-
15	2o	2-Cl	4-Cl	48	No reaction	-	-

[a] *R_f was determined in n-hexane/ethyl acetate the ratio 4:1*



Scheme 4: Probable mechanism for this reaction.



***Scheme 5*: Recovery effect on catalytic reaction.**

and excellent yield (50-97%) obtained for corresponding compounds.

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