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$FeCl_3/SiO_2$ NPs as a robust and efficient catalyst for the synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones

Esmaeil Afkhami and Javad Safaei-Ghomi*

Department of Chemistry, Faculty of Science, Qom Branch, Islamic Azad University, Qom, Iran

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A four-component reaction of phenylhydrazines, ethyl acetoacetate, aldehydes and β-naphthol has been achieved in the presence of $FeCl_3/SiO_2$ nanoparticles as a highly effective heterogeneous catalyst to produce 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones in good to excellent yields, short reaction times, mild reaction conditions and the employment of a cost-effective catalyst.

1. Introduction

The pyrazolone ring system is a structural component of a large number of biologically active compounds. The pyrazolone derivatives are acknowledged to possess a wide range of bioactivities and exhibit important biological properties such as inhibitors of *Mycobacterium tuberculosis*,[1] analgesic activity,[2] antipyretic,[3] antibacterial against Gram-positive and Gram-negative bacteria.[4] Therefore, the development of novel, simple and clean synthetic methods for the synthesis of pyrazolones is an important challenge. Undoubtedly, the synthesis of pyrazolones through multicomponent reactions (MCR) has been paid much attention owing to procedural simplicity, atom economy and generates molecular complexity starting from simple substrates. Hence, synthetic organic chemists have increasingly focused on the use of MCRs to synthesize a broad range of products.[5-8] The combination of multicomponent reactions with a heterogeneous catalyst could improve their effectiveness from operating cost and environmental points of view. Meanwhile, the nature of the catalyst plays a noteworthy role in determining yield, time and selectivity of the reaction. Thus, development of a green, mild, reusable, and general catalyst for MCRs is an interesting challenge. In recent years, the use of

* Corresponding author.
E-mail address: safaei@kashanu.ac.ir (J. Safaei-Ghomi)

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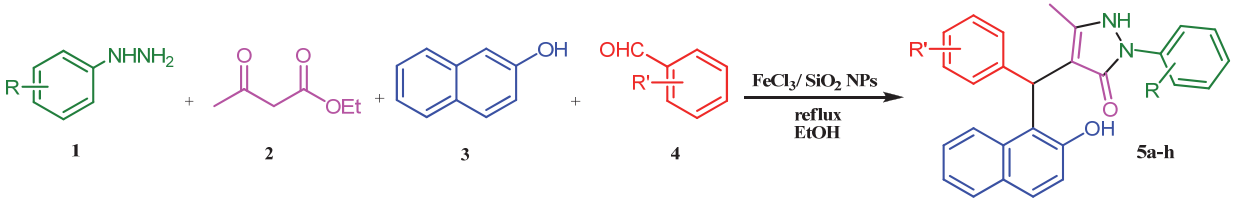
heterogeneous catalysts has provided significant advantages in multicomponent reactions, such as shorter time, saving energy, facile catalyst separation and recycling. These advances have opened the door for the design of new nanocatalysts for specific applications in synthetic chemistry. Recently, nanoparticle catalysts have emerged as an alternative method for the development of many considerable organic reactions. Nano-catalysts decrease reaction times and they can be easily recovered from the reaction mixture by standard techniques (filtration, centrifugation) and recycle without losing their activity.[9-17] In comparison with conventional supports like solid-phase, nanoparticular matrixes have a higher catalyst loading capacity owing to their very large surface area. Among various solid supports, nano silica gel is one of the extensively used surface material supports for different chemical transformations in organic chemistry. Recently, silica-supported Lewis acid has been used as an efficient heterogeneous catalyst for the synthesis 1, 4-dihydropyridines,[18] xanthenes,[19] 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones,[20] 2-aryl-2,3-dihydroquinolin-4(1H)-ones,[21] and 5-substituted 1H-tetrazoles.[22] We report herein a simple and facile procedure for the synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones through one-pot four-component reaction of phenylhydrazines , ethyl acetoacetate, aldehyde and β-naphthol catalyzed by $FeCl_3/SiO_2$ NPs under reflux conditions in ethanol (Scheme 1). Recently, the synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones has been reported using MCRs in the presence of *p*-TSA, [23] and CuI nanoparticles under ultrasonic irradiation.[24]



Scheme 1. Synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones by $FeCl_3/SiO_2$ NPs

2. Results and Discussion

The model reactions were carried out in the presence of various catalysts, such as Na_2SO_4, K10 clay, ZrO_2, SiO_2 NPs and $FeCl_3/SiO_2$ NPs. During the systematic evaluation of different catalysts efficiency in the reaction of phenyl hydrazine, ethyl acetoacetate, β-naphthol and 4-nitrobenzaldehyde we found that $FeCl_3/SiO_2$ NPs catalyst was extremely active in this reaction. In the absence of $FeCl_3/SiO_2$ NPs, the product was obtained in very low yield after prolonged reaction time. When 1, 3, and 6 mol% of $FeCl_3/SiO_2$ NPs were used, the yields were 82, 85, and 85% respectively. Therefore, performing the reaction with a higher catalyst loading (6 mol%) had no significant effect on yield. When the reaction was carried out using ZrO_2 and $FeCl_3/SiO_2$ NPs as the catalyst, the product has been obtained in moderate to good yield. The SEM image of $FeCl_3/SiO_2$ NPs was shown in Figure 1. The SEM image shows particles with diameters in the range of nanometers.

Table 1. The model reaction was carried out by various catalyst under reflux conditions in ethanol [a]

Entry	Catalyst	mol%	Time(h)	Yield[b]%
1	CH_3COOH	10	8	12
2	Na_2SO_4	10	7.5	22
3	K10 clay	2	6.5	38
4	$FeCl_3$	5	5	40
5	ZrO_2	2	5	44
6	SnO	5	4	32
7	SiO_2 NPs	3	4	48
8	$FeCl_3/SiO_2$ NPs	1	2.5	82
9	$FeCl_3/SiO_2$ NPs	**3**	**2**	**85**
10	$FeCl_3/SiO_2$ NPs	6	2	85

[a]Phenyl hydrazine, ethyl acetoacetate , β-naphthol and 4-nitrobenzaldehyde
[b]Isolated yield

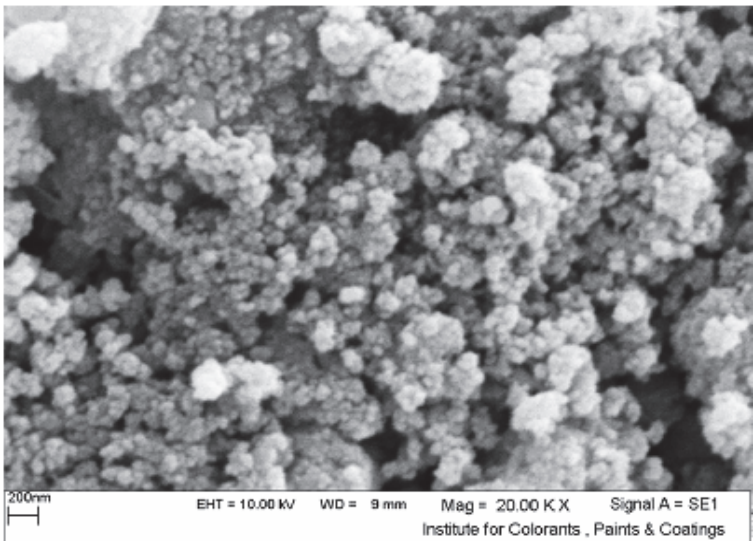
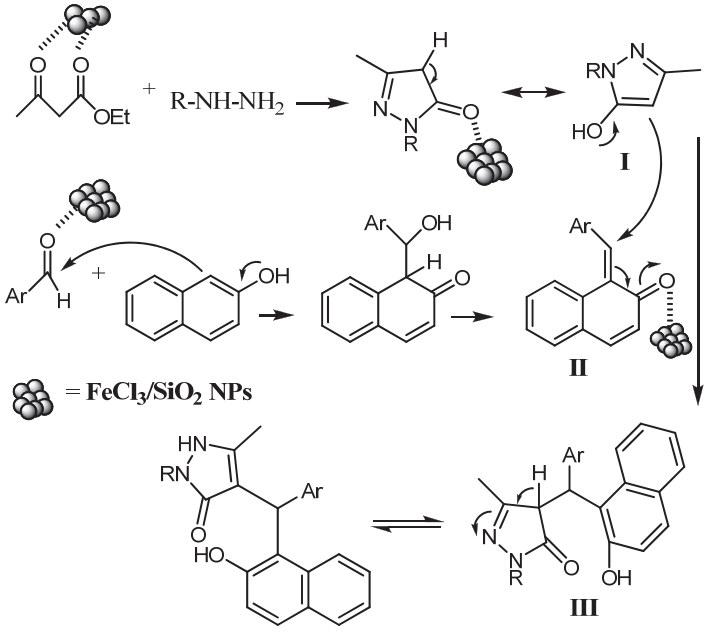


Fig. 1. SEM images of $FeCl_3/SiO_2$ NPs

Almost all reactions with a variety of aromatic aldehydes were successful and the desired compounds were obtained in good to high yields (Table 2). As represented in Table 2, all aldehydes gave the expected products at high yields, either bearing electron-withdrawing groups or electron-donating groups. A proposed mechanism for this four-component reaction was outlined in Scheme 2. The first step of this reaction can be visualized by activation of ethyl acetoacetate1with $FeCl_3/SiO_2$ NPs, following by nucleophilic attack of phenylhydrazine to give **I.** Meanwhile, β-naphthol undergoes condensation with aldehyde in presence of $FeCl_3/SiO_2$ NPs to afford α, β-unsaturated carbonyl compound **II**. Michael addition reaction between compounds **I** and **II** gives intermediate **III** to afford product.



Scheme 2. Possible mechanism for the formation of pyrazolones in the presence of $FeCl_3/SiO_2$ NPs

Table 2. Synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones

Entry	Product	R´	R	Time, min	Yield, %
1	5a	H	H	130	82
2	5b	4-OMe	H	140	78
3	5c	4-NO2	4-Cl	120	82
4	5d	4-Br	4-Cl	128	81
5	5e	4-Cl	H	125	83
6	5f	4-NO2	H	120	85
7	5g	4-Me	H	134	77
8	5h	4-Cl	4-Cl	128	82

We also investigated recycling of the $FeCl_3/SiO_2$ NPs catalyst. The results showed that $FeCl_3/SiO_2$ NPs can be recycled several times without noticeable loss of catalytic activity (yields 85 to 82%) (Figure. 2). The recovered catalyst from the experiment was washed by acetone (3 ×6 mL). Then, it was dried in an oven at 100 °C and used in the synthesis of pyrazolones. Then the catalyst was recycled for five times.

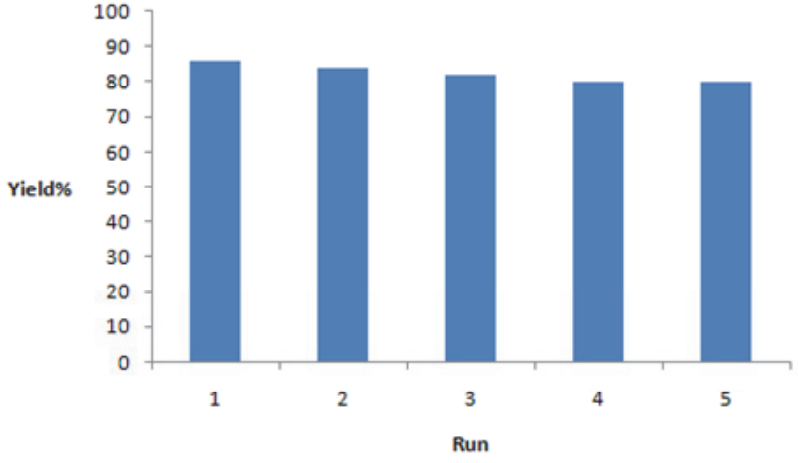


Fig. 2. Recycling of $FeCl_3/SiO_2$ NPs catalyst for the preparation of **5f**

3. Conclusions

In summary, we have developed the synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones in the presence of $FeCl_3/SiO_2$ NPs as a highly effective heterogeneous catalyst under reflux conditions in ethanol. These 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones compounds will provide promising candidates for chemical biology and drug discovery. The advantages offered by this method include, easy workup, the employment of a cost-effective catalyst, short reaction times, excellent yields and recovery and of the catalyst.

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4. Experimental

4.1. Materials and Methods

All reagents were purchased from Merck and Aldrich and used without further purification. The reactions were monitored by TLC using 0.2-mm Merck silica gel 60 F254 pre-coated plates, which were visualized with UV light. Melting points were measured on an Electrothermal 9200 apparatus. The IR spectra were recorded on an FT-IR Magna 550 apparatus using KBr discs.^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-400 instrument using TMS as the internal standard. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Microscopic morphology of products was examined by SEM (LEO 1455VP).

4.2.1. Preparation of Nano Silica-supported Ferric Chloride

Nano silica gel (25 g) and $FeCl_3.6H_2O$ (2 g) (8 % of the weight of nano-SiO_2) were vigorously stirred under solvent-free conditions at room temperature for 24 h to achieve a homogeneous adsorption. A yellowish powder was obtained. This powder was heated for 1 h at100 °C to give a brownish powder ('active' $FeCl_3$-SiO_2 reagent).

*4.2.2. General procedure for the synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones (**5a-h**)*

A solution of phenylhydrazine (1 mmol) ethyl acetoacetate (1 mmol) and $FeCl_3/SiO_2$ NPs (3 mol%) in ethanol (4 ml) was stirred at room temperature for 15 min. Then aromatic aldehyde (1 mmol), β-naphthol (1 mmol) were added and heated to reflux for the appropriate times (monitored by TLC). After completion of reaction the solid was filtered off and washed with chloroform. The residue was dissolved in hot ethanol and then filtered until heterogeneous catalyst was recovered. The ethanol was evaporated and the solid was recrystallized from ethanol to get pure product. The structures of the products were fully established on the basis of their ^{1}H NMR, ^{13}C NMR and FT-IR spectra.

4.3. Physical and Spectral Data

4-[(2-Hydroxy-1-naphthyl)(phenyl)methyl]-5-methyl-2-phenyl-2,3-dihydro-1*H*-3-pyrazolone (5a): White solid; m.p 205–206°C; FT-IR (KBr): 3417, 3162, 3083, 2911, 1612, 1593, 1492, 1412, 1279, 1212, 731, 695 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.12 (s, 3H, CH_3), 6.21 (s, 1H,CH), 7.08 (m, 4H, ArH), 7.13 (m, 2H, ArH), 7.18 (m, 3H, ArH), 7.29 (m, 3H, ArH), 7.31 (s, 1H, NH), 7.71 (m, 3H, ArH), 8.23 (s, 1H, ArH), 10.83 (brs, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 16.6, 40.9, 124.6, 125.3, 126.1, 127.4, 128.2, 130.5, 130.9, 131.6, 132.2, 133.0, 133.6, 133.8, 133.9, 134.2, 136.2, 138.9, 141.6, 146.8, 153.4, 159.1; Anal. Calcd. for $C_{27}H_{22}N_2O_2$: C, 79.78; H, 5.46; N, 6.89; Found: C, 79.74; H, 5.51; N, 6.85.

4-[(2-Hydroxy-1-naphthyl)(4-methoxyphenyl)methyl]-5-methyl-2-phenyl-2,3-dihydro-1*H*-3-pyrazolone (5b): White solid; m.p 180–181°C; FT-IR (KBr): 3422, 3153, 3092, 2944, 1619, 1593, 1487, 1418, 1293, 815, 735, 685 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.13 (s, 3H, CH_3), 3.59 (s, 3H, OCH_3), 6.12 (s, 1H, CH), 6.77 (m, 2H, ArH), 6.95 (m, 2H, ArH), 7.08 (m, 1H, ArH), 7.23 (m, 2H, ArH),7.35 (s, 1H, NH), 7.46 (m, 3H, ArH), 7.68 (m, 3H, ArH), 7.79 (m, 1H, ArH), 8.19 (s, 1H, ArH), 10.86 (brs, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 14.7, 34.4, 54.8, 106.6, 112.8, 119.1, 120.6, 121.8, 122.4, 124.9, 125.7, 128.2, 128.4, 128.5, 128.6, 132.6, 133.4, 133.6, 136.1, 147.5, 148.6, 153.2, 156.7; Anal. Calcd. for $C_{28}H_{24}N_2O_3$: C, 77.04; H, 5.54; N, 6.42; Found: C, 76.98; H, 5.48; N, 6.45.

2-(4-chlorophenyl)-1,2-dihydro-4-((2-hydroxynaphthalen-1-yl)(4-nitrophenyl)methyl)-5-methyl pyrazol-3-one (5c): White solid; m.p = 183–184°C; FT-IR (KBr): 3432, 3088, 2917, 1618, 1596, 1495,

1343, 814, 756, 734, 690, 597 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.19 (s, 3H, CH_3), 6.31 (s,1H, CH), 7.14 (m, 1H, ArH), 7.29 (s, 1H, NH), 7.33 (m, 3H, ArH), 7.46 (m, 1H, ArH),7.56 (m, 2H, ArH), 7.71 (m, 5H, ArH), 8.14 (m, 1H, ArH), 8.26 (m, 1H, ArH), 10.73 (brs, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 16.9, 40.8, 120.7, 121.4, 124.6, 125.9, 127.0, 127.2, 127.7, 128.3, 131.6, 133.5, 133.8, 134.2, 134.8, 138.2, 139.9, 149.6, 152.5, 153.7, 158.5, 159.2; 163.1. Anal. Calcd. for $C_{27}H_{20}ClN_3O_4$: C, 66.74; H, 4.15; N, 8.65; Found: C, 66.69; H, 4.10; N, 8.57.

4-((4-bromophenyl)(2-hydroxynaphthalen-1-yl)methyl)-2-(4-chlorophenyl)-1,2-dihydro-5-methyl pyrazol-3-one (5d): Yellowish solid; m.p 157–158°C; FT-IR (KBr): 3419, 3145, 3085, 2969, 1628, 1585, 1472, 1413, 1274, 816, 805, 736, 691 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.14 (s, 3H, CH_3), 6.12 (s, 1H, CH), 7.05 (m, 5H, ArH), 7.08 (s, 1H, NH),7.21 (m, 2H, ArH), 7.29 (m, 2H, ArH), 7.36 (t, 1H, ArH), 7.56 (t, 1H, ArH), 7.71 (d, 1H, ArH), 7.83 (d, 1H, ArH), 8.03 (d, 1H, ArH), 10.75 (brs, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 14.7, 36.4, 106.4, 120.2, 121.5, 122.2, 123.4, 126.7, 127.2, 127.6,128.4, 128.7, 128.9, 129.1, 129.2, 129.6, 131.4, 131.9, 133.5, 134.9, 138.6, 146.2, 153.9; Anal. Calcd. for $C_{27}H_{20}BrClN_2O_2$: C, 62.39; H, 3.88; N, 5.39; Found: C, 62.37; H, 3.75; N, 5.31.

4-[(4-Chlorophenyl)(2-hydroxy-1-naphthyl)methyl]-5-methyl-2-phenyl-2,3-dihydro-1H-3-pyrazolone (5e): Yellow solid; m.p 174-176°C; FT-IR (KBr): 3392, 3150, 2961, 1625, 1461 cm^{-1}; ^1H NMR(400 MHz, DMSO-d_6) δ (ppm): 2.20 (s, 3H, CH_3), 6.21 (s, 1H, CH), 7.12-7.18 (m, 3H, ArH), 7.22 (s, 1H, NH), 7.27-7.34 (m, 4H, ArH), 7.48-7.54 (m, 3H, ArH), 7.75-7.83 (m, 3H, ArH), 7.89 (d, 1H, *J*= 8.3 Hz, ArH), 8.28 (d, 1H, *J*=8.3 Hz, ArH), 10.85 (bs, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.1, 36.1, 106.2, 119.9, 120.7, 121.3, 122.9, 123.4, 125.7, 126.8, 128.1, 129.0, 129.1, 129.2, 129.4, 129.7, 130.4, 133.5, 133.8, 137.0, 141.2, 148.5, 154.0. Anal. Calcd for $C_{27}H_{21}ClN_2O_2$: C, 73.55; H, 4.80; N, 6.35; Found: C, 73.61; H, 4.85; N, 6.24.

4-[(4-nitrophenyl)(2-hydroxy-1-naphthyl)methyl]-5-methyl-2-phenyl-2,3-dihydro-1H-3-pyrazolone (5f): Yellow solid; m.p 207-209°C; FT-IR (KBr): 3410, 3098, 2920, 1631, 1466 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.23 (s, 3H, CH_3), 6.29 (s, 1H, CH), 7.12-7.16 (m, 1H, ArH), 7.20 (s, 1H, NH), 7.22-7.29 (m, 1H, ArH), 7.30-7.36 (m, 3H, ArH), 7.41-7.48 (m, 3H, ArH), 7.68-7.74 (m, 2H, ArH), 7.76-7.79 (m, 1H, ArH), 7.81-7.85 (m, 1H, ArH), 8.10-8.13 (m, 2H, ArH), 8.20-8.22 (m, 1H, ArH), 10.82 (bs, 1H, OH);^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.0, 36.8, 105.3, 119.9, 120.3, 121.0, 123.0, 123.3, 123.4, 125.7, 126.9, 129.0, 129.1, 129.4, 129.5, 133.5, 133.7, 137.0, 138.2, 146.0, 148.5, 151.5, 153.9. Anal. Calcd for $C_{27}H_{21}N_3O_4$: C, 71.83; H, 4.69; N, 9.31; Found: C, 71.75; H, 4.61; N, 9.25.

4-[(2-Hydroxy-1-naphthyl)(4-methylphenyl)methyl]-5-meth-yl-2-phenyl-2,3-dihydro-1H-3-pyrazolone (5g): White solid; m.p. 178-180°C; FT-IR (KBr): 3433, 3054, 2973, 1618, 1477 cm^{-1}; ^1H NMR(400 MHz, DMSO-d_6) δ (ppm): 2.24 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 6.09 (s, 1H, CH), 7.02-7.09 (m, 4H, ArH), 7.15-7.21 (m, 2H, ArH), 7.30-7.37 (m, 3H, ArH), 7.39 (s, 1H, NH), 7.50 (m, 1H, ArH), 7.69-7.71 (m, 3H, ArH), 7.81 (m, 1H, ArH), 8.15 (d, 1H, *J*= 8.0 Hz, ArH), 10.81 (bs, 1H, OH); ^{13}C NMR (100 MHz DMSO-d_6) δ (ppm): 11.9, 21.2, 35.9, 106.6, 120.2, 121.2, 121.6, 122.5, 125.6, 126.5, 127.4, 128.7, 128.8, 128.9, 129.0, 129.1, 129.8, 133.8, 134.7, 136.6, 138.3, 147.7, 154.1, 161.3. Anal. Calcd for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66; Found: C, 79.89; H, 5.81; N, 6.60.

2-(4-Chlorophenyl)-4-[(4-chlorophenyl)(2-hydroxy-1-naphthyl)methyl]-5-methyl-2,3dihydro-1H-3-pyrazolone (5h): Yellow solid; m.p. 152-154°C; FT-IR (KBr): 3421, 3089, 2987, 1612, 1455, 1274 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.26 (s, 3H, CH_3), 6.09 (s, 1H, CH), 7.01-7.07 (m, 5H, ArH), 7.10 (s, 1H, NH), 7.19-7.24 (m, 2H, ArH), 7.26-7.30 (m, 2H,ArH), 7.36 (t, 1H, *J*=7.0 Hz, ArH), 7.55 (t, 1H, *J* =7.0 Hz, ArH), 7.68 (m, 1H, ArH), 7.82 (m, 1H, ArH), 8.06 (m, 1H, ArH), 10.71 (bs, 1H, OH);^{13}C NMR (100 MHz DMSO-d_6) δ (ppm): 12.9, 35.5, 106.1, 120.0, 121.3, 122.3, 123.1, 126.8, 127.0, 127.7, 128.3, 128.8, 128.9, 129.0, 129.2, 129.5, 131.2, 131.8, 133.4, 134.8, 139.0,

145.6, 153.5. Anal. Calcd for $C_{27}H_{20}Cl_2N_2O_2$: C, 68.22; H, 4.24; N, 5.89; Found: C, 68.28; H, 4.32; N, 5.81.

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