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ARTICLE

Green, efficient and large-scale synthesis of benzimidazoles, benzoxazoles and benzothiazoles derivatives using ligand-free cobalt-nanoparticles: as potential anti-estrogen breast cancer agents, and study of their interactions with estrogen receptor by molecular docking

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A facile and high yielding method for the synthesis of 2-aryl benzoxazoles, benzimidazole and benzothiazoles is reported employing cobalt oxide nanoparticles. The cobalt oxide nanoparticles were used as a convenient, green, easy available and highly efficient heterogeneous nano catalyst which promoted cyclization cross-coupling reactions without ligands and/or additives. This procedure has advantages such as simplicity of work-up, eco-friendly of reaction medium, low cost and mild conditions of reaction. In addition to, the binding modes of synthesized compounds to estrogen receptor were studied by molecular docking to investigate their potentially anti breast cancer activity.

Introduction

Cancer is one of the main causes of death, which ranked only after heart diseases. The most frequently diagnosed cancer in women is breast cancer, especially in industrialized countries.[1-2] Estrogen receptor (ER) are high affinity cell surface receptors in cancerous cells that can bind to polypeptide growth factors, cytokines and hormones. In a breast cancer cell, estrogen activates ERα by binding to its active site, this estrogen–ERα complex further activate the estrogen response element (ERE) on DNA to target genes regulating transcription. As a result, several effects such as cell proliferation in the breast are stimulated.[3-8] However, for breast cancer, the hormone therapy means that the estrogen production can be blocked using synthetic estrogen and, in particular, anti-estrogen ligands and consequently the breast cancer cells are prevented from proliferation. Therefore, it is an attractive pharmaceutical target for the improvement of novel therapeutic agents for the treatment of breast cancer.

According to previous studies, moreover the physicochemical properties of the synthetic ER ligands, molecular shape as expected to be extremely important for the access and interaction with the receptors. The described molecules herein are similar in size, shape and polarity to known compounds which have demonstrated inhibitory activity in the life cycle of both ER-negative and ER-positive breast cancer cells.[9-13]

The benzimidazoles, benzoxazoles and benzothiazoles frameworks are a very valuable class of heterocyclic compounds in the area of drug design; based on reported results, some their derivatives can make good cytotoxic effects on the MCF-7 cell line and have been used widely in the structure of some potent estrogen ligands.[14-21] Therefore, considerable efforts to find new efficient and facile methodologies to improve their synthesis would be logical.

In the past few decades, numerous synthetic strategies for their synthesis have been reported.[22-25] However, the development green and simple methods for synthesis of these compounds remain complicated.

The traditional methods have some limitations such as availability of starting materials and using of either toxic reagents or harsh reaction conditions in a multistep ways,[26-31] hence, to solve these problems, the more appropriate transition-metal-catalyzed cross-coupling reactions were developed. In almost reported methods, the transition metals such as palladium[32-34] and copper[35-48] combined with ligands and additives as homogeneous catalysts.

The homogeneous catalysts, even though high efficiency, are undesirable from an industrial point of view due to non-recoverability. This limitation can be overcome by using nano-crystalline transition metal oxides catalysts, because they usually insoluble in reaction media and can be easily filtered out.

In recent years, among the first-row transition metal catalysts, cobalt catalyst has attracted much attention in organic synthesis; because it is readily available, non-toxic, low-cost, stable in air and exhibits high catalytic activity.[49-57] However, to the best of our knowledge aryl halide-heteroatom cross-

couplings using cobalt salts are rare; catalyst application of cobalt salts combined with ligands have explored as a suitable catalyst for construction of C–N and C–O bonds via dehalogenative paths.[58-59]

In a continuation of our recent investigations on drug desing and studies,[60-64] herein, we would like to report a new green and economical synthesis of benzimidazoles, benzoxazoles and benzothiozole through cross-coupling cyclization reactions using cobalt oxide nanoparticles (Co-NPs) in ligand-free and aerial conditions and evaluation their potential anticancer activities using molecular docking. Molecular docking is one of the more computationally inexpensive methods for predicting strength of the ligand binding affinity to protein binding pocket.[65-71]

Results and discussion

The catalyst of Co-NPs was initially synthesized in aqueous medium via easy and high efficiency method. Morphologies were analysed by field emission scanning electron microscopy (FE-SEM) images (Figure 1). The crystal structure of the catalyst was also characterized by powder X-ray diffraction (XRD) using Cu-Kα irradiation.[72]

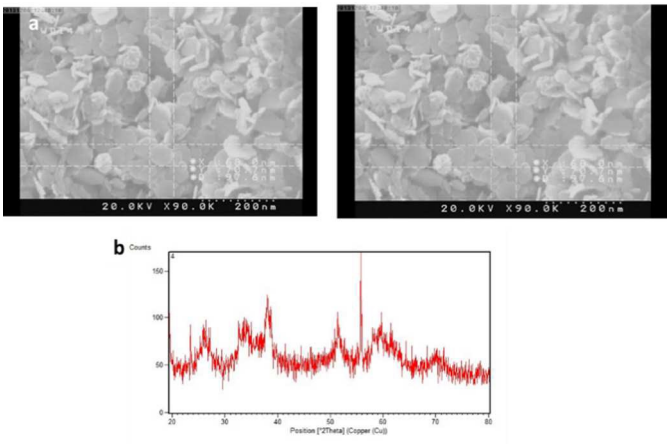


Figure 1. a: FE-SEM images and b: XRD patterns of cobalt oxid nanoparticles

The synthetic cobalt oxide compound is a gray powder, the particles of which are observed by transmission electron microscopy (TEM) (Figure 2).

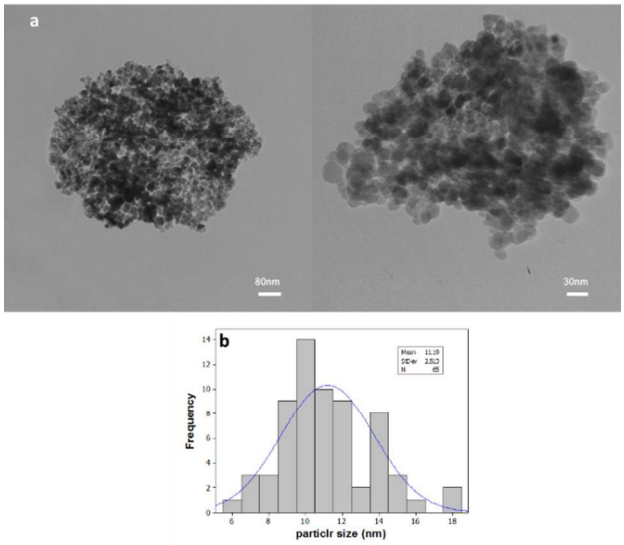


Figure 2. a: TEM images and b: particle size distribution results for cobalt oxid nanoparticles

The size distribution are about 9-12 nm. The experimental procedure for the reaction using Co-NPs catalyst is remarkably simple and does not require to use of toxic or expensive organic solvents or reagents.

Initially, in order to optimize the reaction conditions, *N*-(2-bromo-phenyl)-4-hydroxy-benzamide was chosen as a model substrate. The influence of bases in this reaction was examined and variouse amount of different bases such as KOH, K_2CO_3, K_3PO_4 and NaOH were used and K_2CO_3 (4 eq) was selected as the best base.

Next, the effect of various solvents on the reaction system was studied. It was observed that ethanol was effective in providing higher conversion, whereas DMSO, NMP and solvent free conditions showed lower conversions.

We also examined catalyst amount and 10 mol % of catalyst was found to be optimal. A lower catalyst concentration usually led to slow reactions. However, increasing the catalyst concentration to 20 mol % did not have any further significant effect on the yield or reaction time. The improvement in the conversion (94%) was achieved for the reaction at 80 ºC and in lower reaction temperature (50 ºC and r.t.), the yield decreased to 67% and 55% even after long reaction times. Therefore, all reactions were carried out at 80 ºC (Table1).

Table 1. Optimization studies for the Co-NPs-catalyzed C–O cross-coupling of model reaction.[a]

Entry	Catalyst (mol %)	Solvent	Base (equv.)	Time (h)	T (ºC)	Yield [b] (%)
1	20	DMSO	K_2CO_3 (2)	8	100	90
2	10	DMSO	K_2CO_3 (2)	8	100	87
3	5	DMSO	K_2CO_3 (2)	8	100	64
4	10	NMP	K_2CO_3 (2)	8	100	84
5	10	Solvent free	K_2CO_3 (2)	8	100	83
6	10	EtOH	K_2CO_3 (2)	8	80	92
7	10	EtOH	K_2CO_3 (3)	8	80	90
8	**10**	**EtOH**	**K_2CO_3 (4)**	**8**	**80**	**96**
9	10	EtOH	KOH (4)	8	80	87
10	10	EtOH	NaOH (4)	8	80	80
11	10	EtOH	K_3PO_4 (4)	8	80	63
12	10	EtOH	K_2CO_3 (4)	14	50	67
13	10	EtOH	K_2CO_3 (4)	24	r.t.	55

[a] Reaction conditions: *N*-(2-bromo-phenyl)-4-hydroxy-benzamide (0.7 mmol), catalyst and solvent (2 mL) under air. [b] GC yield

According to the optimization results and the essential goal of green chemistry, the ideal result was obtained by using ethanol (2 mL), Co-NPs (10 mol%) and K_2CO_3 (4equiv) vigorously at 80 ºC. The process of synthesis substituted benzoxazoles, benzothiazoles and benzimidazoles is described in Scheme 1.

The scope of the procedure was explored for the cyclization of the other derivatives. The versatility of current protocol over a broad range of aryl substitutions from weak to strong electron density groups has been investigated. Excellent yields for the synthesized benzoxazoles, benzothiazoles and benzimidazoles were obtained and products were easily isolated via crystallization.

The results are summarized in Table 2, with isolated yields ranging from 83% to 96%. The results clearly show that the reactions of substrates with electron-donating group were faster than those of with electron-withdrawing.

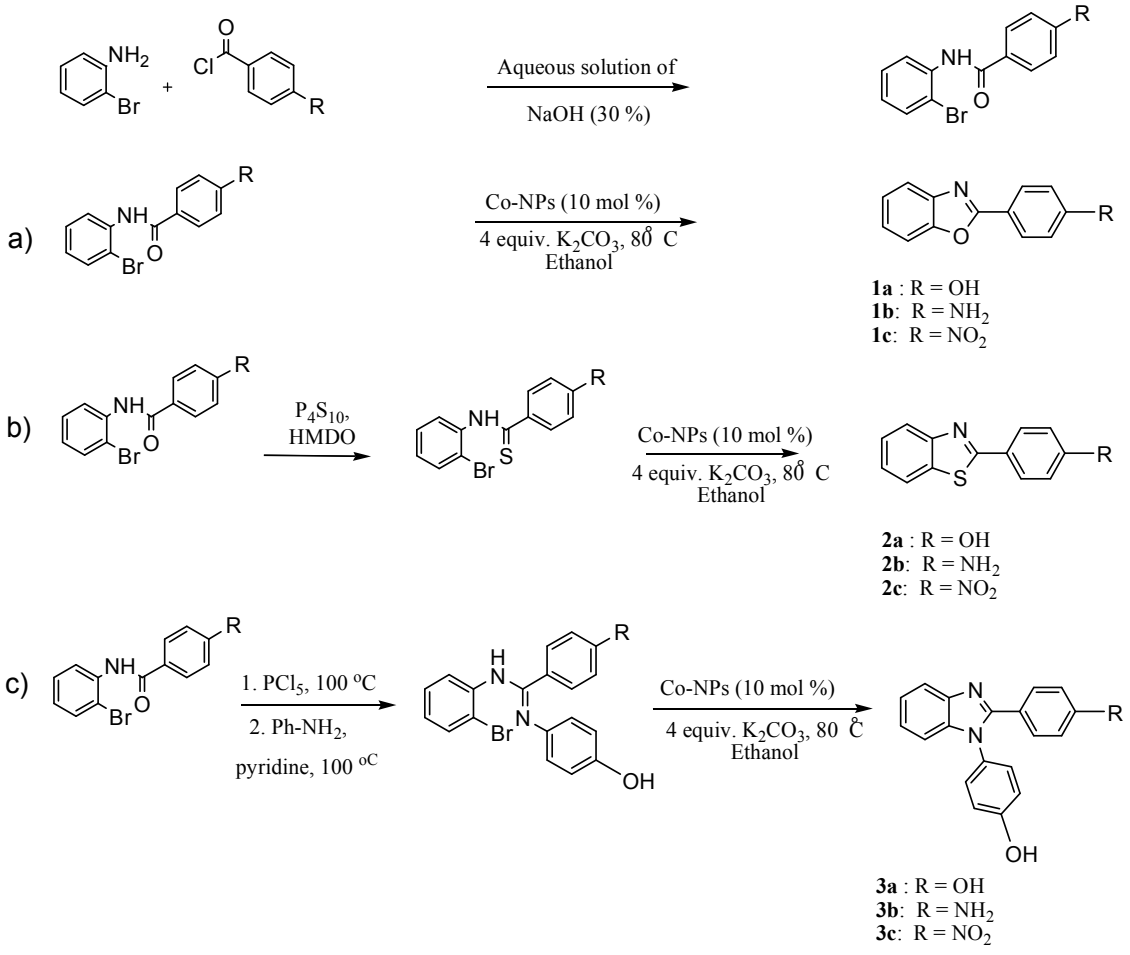
In comparison to the known synthetic methods, Co-NPs catalyst in the majority of reactions presented comparable or even higher activity. For example, in reactions of entries 2-3 and 5-6 (Table 2) using homogenous palladium catalyst the reported yields were 66-78 %. These methods require high temperatures and the products were obtained in moderate yields (Table 2, entries 2-3 and 5-6), while Co-NPs gave these products in good yields (88-94 %) in mild conditions (Table 2, entry 2-3 and 5-6).

All the products were characterized by ^{13}C and ^{1}H NMR, IR and CHN analysis, and also by comparison with authentic samples.

The presumably reaction mechanism has been illustrated in Scheme 2. The base plays a crucial catalytic role in the reaction cycle; Co(0) inserts in carbon-hteroatom bond through oxidative-addition reaction and follows to complete the catalytic cycle by reductive elimination to heterocyclic products.[58]

The recyclability and efficiency of the catalyst in scale-up synthesis are key parameters for industrial and commercial uses of any catalytic operations. The Co-NPs not only exhibits excellent activity in this reaction, but also recycles and reuses to simplify.

As reported in Table 3, the catalyst was reused several times (five consecutive runs were checked) without significant losing in activity. In continuous, the scale of the reaction was increased to 10.0 mmol, keeping the reaction stoichiometry intact. The reaction was found to proceed successfully, and the corresponding product was obtained in 91% yield via described method respectively.



Scheme 1. Synthesis of derivaties of benzoxazoles(a), benzothiozoles (b) and benzimidazoles (c), catalyzed by Co-NPs.

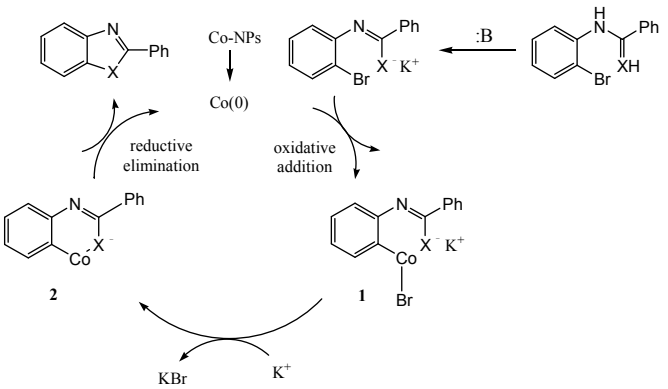
Table 2. Scope of Co-NPs-catalyzed intramolecular C–N, C-O and C-S cross-coupling [a]

Entry	R	Products	Time (h)	Yield [b] (%)	Reported methods			Ref.
					Metal cat., T (ºC)	Time (h)	Yield (%)	
1	-OH	**1a**	8	96	-	-	-	-
2	$-NH_2$	**1b**	8	92	Pd (150)	1	66	67
3	$-NO_2$	**1c**	8	87	Pd (75)	4	78	27
4	-OH	**2a**	8	96	-	-	-	-
5	$-NH_2$	**2b**	8	94	Pd (150)	1	68	67
6	$-NO_2$	**2c**	8	88	Pd (75)	8	75	27
7	-OH	**3a**	6	91	-	-	-	-
8	$-NH_2$	**3b**	6	79	-	-	-	-
9	$-NO_2$	**3c**	6	83	-	-	-	-

[a] Reaction conditions: substrate (1.0 mmol), Co-NPs catalyst (10 mol %), K_2CO_3 (4 equiv.) and refluxing in EtOH (2 mL) under air.

[b] Isolated yield

[c] Traditional or intramolecular cross-coupling methods



Scheme 2. The presumably mechanism of reaction

Table 3. Recyclability of Co-NPs

Run	Yield [a] (%)	Run	Yield [a] (%)
1	95	4	88
2	92	5	83
3	89	-	-

[a] Isolated yield

Ligand and Protein preparation for docking

The database of 9 natural structures used in our molecular docking studies. They have been optimized in the gas phase using Gaussian 09 program[73] by B3lyp/6-31g(d,p) level of theory. The three dimensional structure of the complex NF-kappaB-DNA[74] (PDB code: 1NFK) was retrieved from the Brookhaven protein database (RCSB) (http://www.rcsb.org). The co-crystallized DNA macromolecule was removed from the pdb structure. p50 dimer and p50 monomers (chains A and B) were chosen for the docking simulations. All water molecules were removed, the hydrogen atoms were added to the proteins and all atom force field (OPSL-2001) charges and atom types were allotted.

Docking Study

All docking simulations were done by means of an in house batch script (DOCKFACE) for automatic running of Autodock4.2[75] in a parallel mode by all system resources. To facilitate docking studies, DOCKFACE was designed in stepwise mode including ligand preparation, receptor preparation, conf.txt preparation and finalization of docking runs. To find the best pose of each ligand in the active site of the target protein, in all experiments genetic algorithm search method was utilized.[76] The 3-D grid box has been made with a grid centre co-ordinates comprising of grid spacing 0.375 Å and 60 ×60 ×60 point size perceiving active site residues included within it and coordinates of the grid center were -1.1958, 9.0149, and 19.7598 respectively. Random orientations of the conformations were produced after translating the center of the ligand to a specified position within the receptor active site. No attempt was prepared to minimize the ligand-receptor complex (rigid docking). VMD software was used for visualization of protein ligand complexes.[77]
benzimidazoles moieties and their substitutions with estrogen receptor protein . The molecular docking results was given in Table 4.

Table 4. The calculated free binding energies of the synthesized ligands with estrogen receptor along with the the name of interacting residue.

Ligand	Binding Energy (kcal mol^{-1})	Hydrogen bonding and π-π interaction residues	Min (max) rmsd (ºA)
1a	-5.69	Arg(B54), Glu(B60), His(B141)	0.01(1.02)
1b	-5.47	Glu(B60), His(B141)	0.04(0.89)
1c	-6.68	---	0.01(0.83)
2a	-5.76	Arg(B54), Glu(B60), Tyr(B57), His(B141)	0.01(1.39)
2b	-5.87	Glu(B60), His(B141)	0.02(1.36)
2c	-6.84	---	0.01(1.21)
3a	-5.49	His(B141), Phe(B55), Asp(B239), Lys(B272)	0.04(1.45)
3b	-5.53	Phe(B55), Arg(B54), Asp(B239), Tyr(B57)	0.03(1.58)
3c	**-7.40**	**Asp(B239), Lys(B272), His(B141)**	**0.06(0.52)**

The synthesized compounds could make the hydrophobic interactions through their benzoxazoles, benzothiazoles and Examination of the best-ranked docking reveals that among the three heteroaromatic rings located in the substrate cavity, the 3c was the best from the docking results relatively, which its interaction shown in Figure 4. All of the docking molecular intraction images was given in supplemental material.
The compound 3c in which there is 4-nitro and 4-hydroxy substitution on the phenyl ring, has showed better binding energy to ER (Table 4) compared with some reported potential ERs ligands. Additionally, hydrogen bonding π–π conjugate interactions are formed among Asp(B239), Lys(B272), His(B141) the phenyl ring of N-(2-bromo-phenyl)-N'-(4-hydroxy-phenyl)-benzamidine. Compounds having the oxygen heteroatom and only hydroxyl substitution were found to be less active as compared to other compounds.
The bio-assay of anticancer bioactivities of these compounds will be performed in the future research.

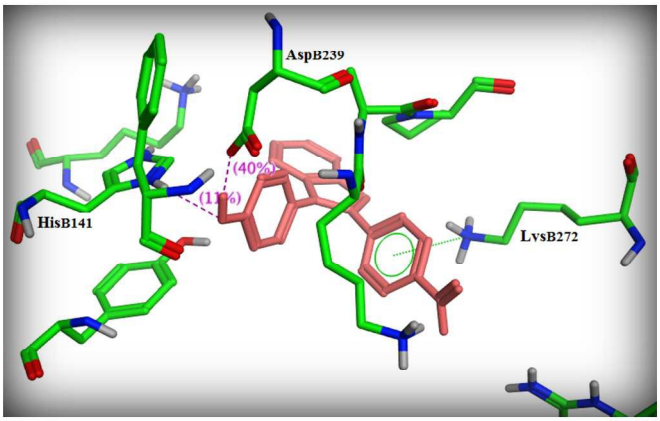


Figure 3. Superposition of the docked poses of the best synthesized ligand in the active site

Conclusions

In summary, three distinct reaction paths have been reported to favour the metal catalyzed transformation over the intramolecular ring closure. The present Co-catalyzed approach provides a green way to synthesis these important products without need to ligands, oxidants, additives, or hazardous solvents. The use of an environmentally friendly solvent (ethanol) and a recyclable catalyst make this procedure a benign alternative to the existing methods of three interesting classes of molecules, benzoxazoles, benzothiazoles and benzimidazoles.
A total of 9 compounds were synthesized and screened for anticancer activity. The binding modes of all of the compounds at the binding site on estrogen receptor have been investigated utilizing molecular docking studies. These compounds are ranked through the potency of ligand as inhibitors of estrogen activity.

Experimental

General for preparation of cobalt oxide nanoparticles (Co-NPs)

In a typical procedure, a solution of 0.5 M (10 mL) of cobalt sulphate was prepared using dematerialized water. Then, required amount of hydrazine (2 M, 10 mL) and NaOH solution (10 mL, 60%) was added in sequence. The entire Co^{2+} ion in the solution was allowed to precipitate under ultra-sonication process. The reduced black powder was washed thoroughly with dilute HCl to remove traces of alkali and finally with ethanol, dried under vacuum at 50 ºC for overnight.

General procedure for cyclization reactions

Benzoxazole: In a round-bottomed flask equipped with a condenser and a magnetic stirrer, 2-bromoaniline (172 mg, 1 mmol) and 4-hydroxy-benzoyl chloride (166 µL, 1.5 mmol, reacted together in aqueous sodium hydroxide (10 mL, 30 %) to obtain bromoamids. *N*-(2-bromo-phenyl)-4-hydroxy-benzamide (204 mg, 0.7 mmol) K_2CO_3 (207 mg, 1.5 mmol) and cobalt nanostructure (5 mg, 10 mol%) was stirred in ethanol (2 mL) under air atmosphere for the appropriate time (Table 2). The progress of the reaction was monitored by TLC (eluent: n-hexane /ethyl acetate, 4:1). After completion of the reaction CH_2Cl_2 (15 mL) was added and the catalyst was separated by centrifuge. The catalyst was washed and dried. The residue was purified by recrystallization from ethanol to obtain the corresponding products in 87-95 % yields.

Benzothiazole: In a round-bottomed flask equipped with a condenser and a magnetic stirrer, 2-bromoaniline (172 mg, 1 mmol) and 4-hydroxy-benzoyl chloride (166 µL, 1.5 mmol), reacted together in aqueous sodium hydroxide (10 mL, 30 mol%) to obtain bromoamids; Next, *N*-(2-bromo-phenyl)-4-hydroxy-benzamide (204 mg, 0.7 mmol) was dispersed in toluene (15 mL), and hexamethyldisiloxane (HMDO) (162 mg, 1.0 mmol) was added with stirring. The mixture was heated to 60 °C, phosphorus pentasulfide (220 mg, 0.5 mmol) was added with further toluene (5 mL), and then the mixture was heated under reflux for 5 h. After cooling, toluene was evaporated under reduced pressure. The product was purified by column chromatography (hexane: ethyl acetate 3:2) to give desired product as a yellow-orange solid. *N*-(2-Bromo-phenyl)-4-hydroxy-thiobenzamide (154mg, 0.5 mmol), K_2CO_3 (207 mg, 1.5 mmol) and cobalt nanostructure (4 mg, 10 mol%) was stirred in ethanol (2 mL) under air atmosphere for the appropriate time (Table 2). The progress of the reaction was monitored by TLC (eluent: n-hexane /ethyl acetate, 4:1). After completion of the reaction CH_2Cl_2 (15 mL) was added and the catalyst was separated by centrifuge. The catalyst was washed and dried. The residue was purified by recrystallization from ethanol to obtain the corresponding products in 88-96 % yields.

Benzimidazole: In a round-bottomed flask equipped with a condenser and a magnetic stirrer, 2-bromoaniline (0.172 g, 1 mmol) and 4-hydroxy-benzoyl chloride (166 µL, 1.5 mmol) reacted together to obtain bromoamids. In a round bottom flask, p-toluenesulfonic acid (10 mg, 6 mol%) was slowly added to a mixture of a *N*-(2-bromo-phenyl)-4-hydroxy-benzamide (203 mg, 0.7 mmol) and 4-amino-phenol (109 mg, 1.0 mmol) in 2 mL EtOH. The resulting mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. The product was obtained upon recrystallization. *N*-(2-Bromo-phenyl)-*N*'-(4-hydroxy-phenyl)-benzamidine (183 mg, 0.5 mmol), K_2CO_3 (207 mg, 1.5 mmol) and cobalt nanostructure (4 mg, 10 mol %) was added to reaction mixture and refluxed in ethanol (2 mL) under air atmosphere. The progress of the reaction was monitored by TLC (eluent: n-

hexane /ethyl acetate, 4:1). After completion of the reaction, the resulting mixture was diluted with ethyl acetate, and washed with brine. The organic layer was dried and concentrated under vacuum. The resulting residue was separated by silica gel column (eluent: n-hexane /ethyl acetate, 9:1) to yield final compounds (83-91%).

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Notes and references

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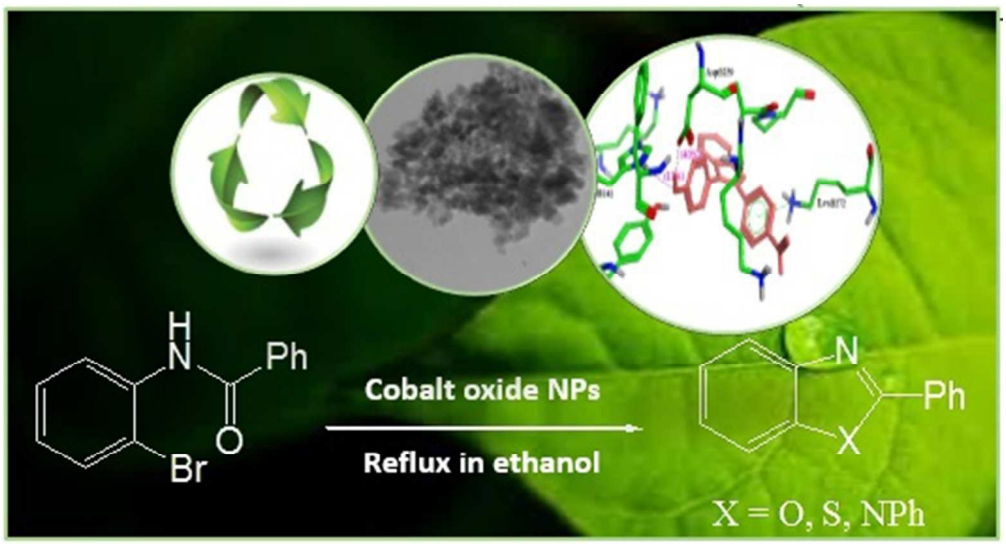

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