Fe_2O_3 as an Environmentally Benign Natural Catalyst for One-Pot and Solvent-Free Synthesis of Spiro-4*H*-Pyran Derivatives

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ABSTRACT: *In this work, a simple and economical procedure for the synthesis of spiro-4H-pyran derivatives has been found through the three-component, one-pot condensation of isatin/acenaphthequinone, malononitrile and different reagents including 1, 3-dicrbonyl compounds, naphthol and 4-hydroxycumarin under thermal and solvent-free conditions in the presence of Fe_2O_3 as an efficient catalyst. The major advantages of this methodology are mild reaction conditions, eco-friendly, environmentally benign, non-toxic and inexpensive catalyst, experimentally simplicity, good yields and short reaction times.*

KEYWORDS: *Fe_2O_3 (ferric oxide); Spiro-4H-pyran derivatives; Solvent-free condition; One-pot reaction.*

INTRODUCTION

During the past decades, multi-component reactions (MCRs) [1-8] have become the main aim of the organic researches in the synthesis of heterocyclic compounds because of their specially benefits such as one-pot, simple work-up, eco-friendly, mild and environmentally-friendly and low-cost.

In the recent years, the spiro-4*H*-pyran derivatives have attracted considerable attention in organic synthesis because the show some biological activities (Fig. 1) and pharmacological properties for example anticancer [9], anticonvulsant [10], fungicidal [11], anti HIV [12], antimalarial [13], antitubercular [14], in addition these spirocycles are MDM2 inhibitor [15] and progesterone receptor modulator [16].

Because of their biological and pharmaceutical activities spiro-4*H*-pyran derivatives, several methodology including various catalysts for the synthesis of these fused heterocyclic compounds is reported such as carbon-SO_3H [17], $[BMIm]BF_4$ [18], urea-choline chloride [19], sulfated choline based heteropolyanion [20], Et_3N [21], L-proline [22], ethylenediaminediaceticacid [23], β-cyclodextrin [24], lipase [25], $InCl_3$ [26], CsF [27], DMAP [28], HTM [29], MgO nanocrystalline [30]. Some of disadvantages these

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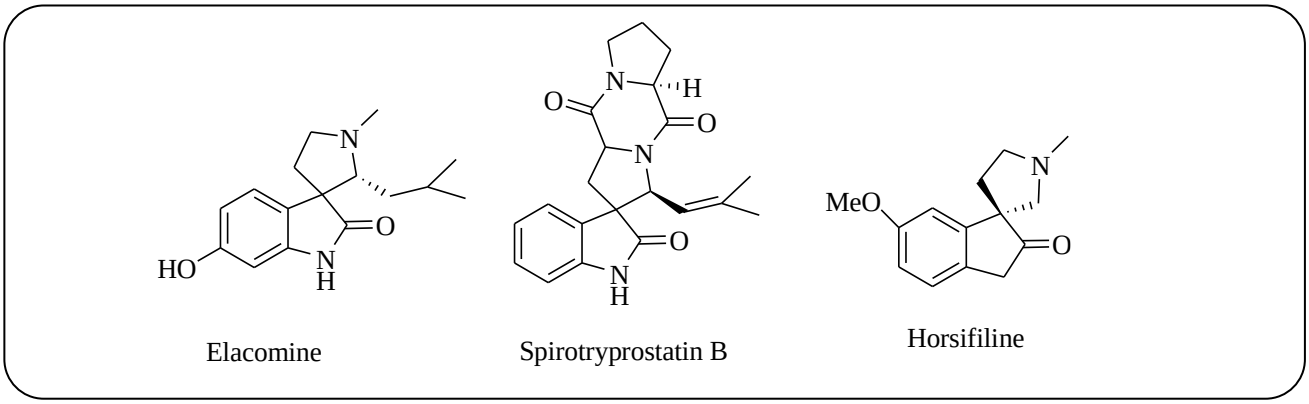


Fig. 1: Some alkaloids containing heterocyclic spirooxindole unit.

methodologies are toxic and expensive catalysts and solvents, long time reactions, low yields and difficulty work-up.

The major source of environmental pollutions are the usage of organic solvents in organic synthesis. Therefore, we had interested work on developing on multi-component reactions with reduction of amount of organic solvents and the developing of designing multi-component reactions under solvent-free conditions has become the chief of goal our researches. Because of the above considerations and our interest in the development of synthesis of spiro-4*H*-pyran derivatives we have studied of the development of clean, simple and environmentally friendly approaches for the synthesis of these fused heterocyclic compounds and finally, we have reported a simple, mild and economical method for one-pot three-component condensation reaction of isatin/acenaphthequinone, malononitrile and different reagents including 1,3-dicrbonyl compounds, naphthol and 4-hydroxycumarin under thermal and solvent-free conditions in the presence of Fe_2O_3 (ferric oxide) as an efficient catalyst with excellent yields and short reaction times.

EXPERIMENTAL SECTION

General

Melting points and IR spectra all compounds were determined using an Electro thermal 9100 apparatus and a JASCO FTIR 460 Plus spectrometer. Also, ^{1}H NMR spectra were recorded on a Bruker DRX-400 Avance instruments with DMSO-d_6 as solvents. All reagents and solvents in this article, were purchased from Merck, Fluka and Acros chemical companies were used without further purification.

General procedure for preparation of spirooxindole and spiroacenaphthylene derivatives (4a-f) and (8a-f)

A mixture of isatin/acenaphthequinone (1.0 mmol), malononitrile (1.0 mmol) and different reagents including [1,3-dicrbonyl compounds, naphthol and 4-hydroxycumarin] (1.0 mmol) in the present of Fe_2O_3 (20 mol %) at 90 ºC and solvent-free conditions was heated for the appropriate time. After completion of the reaction by thin layer chromatography (TLC), the mixture was cooled to r.t. and ethanol was added and the precipitated was separated with filtration and solid was recrystallized from ethanol to afford the pure products (**4a-f**) and (**7a-f**). All products were characterized by comparison of spectroscopic data (FT-IR, ^{1}HNMR). Spectra data of selected and known products are represented below:

7-Amino-1,3-dimethyl-5-nitro-2,2,4-trioxo-1,2,3,4-tetra-hydrospiro[indoline-3,5- pyrano[2,3-d]pyrimidine] -6-carbonitrile (4a)

^{1}H NMR (400 MHz, DMSO-d_6): 1.00 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.07-2.19 (2H, m, CH_2), 2.50-2.57 (2H, m, CH_2), 6.79 (1H, d, *J*=7.2 Hz, ArH), 6.89 (1H, t, *J*=7.2 Hz, ArH), 6.98 (1H, d, *J*=6.8 Hz, ArH), 7.13 (1H, t, *J*=6.4 Hz, ArH), 7.22 (2H, s, NH_2), 10.38 (1H, s, NH).

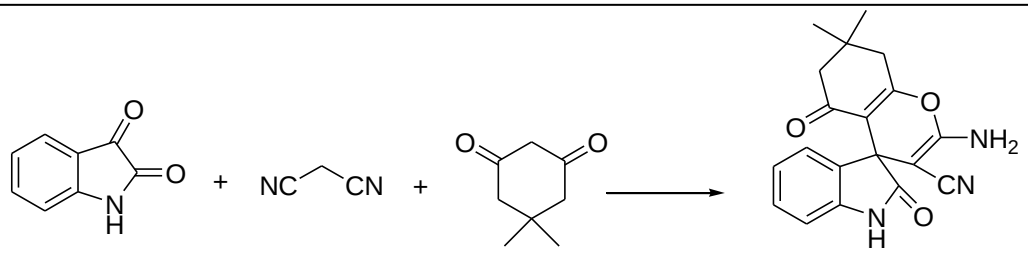
2-Amino -7,7- dimethyl -2,5,6,7,8- tetrahydro-2H-spiro[acenaphthylene-1,4-chromene]-3-carbonitrile (7a)

^{1}H NMR (400 MHz, DMSO-d_6): 1.02 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.04-2.13 (1H, m, CH_2), 2.50-2.51 (1H, m, CH_2), 2.63 (2H, s, CH_2), 7.32 (2H, s, NH_2), 7.37-7.85 (6H, m, ArH).

RESULTS AND DISCUSSION

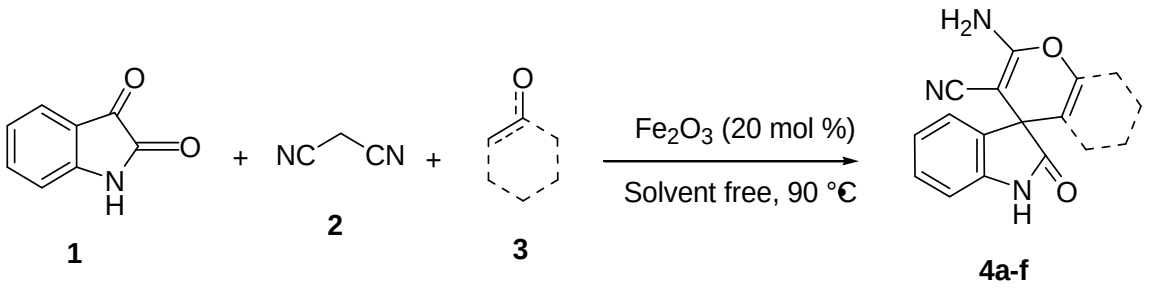
An efficient catalyst for one-pot, economical, simple synthesis of spirooxindole derivatives via isatin (**1**, 1.0 mmol),

Table 1: Optimization of the reaction condition for the synthesis of spir-4H-pyran-3,3-oxindole] [a].



Entry	Fe_2O_3 (mol %)	Time (h)	Product	Isolated Yields (%)
1	Catalyst free	10	4a	Not product
2	5	10	4a	38
3	10	7	4a	47
4	15	5	4a	64
5	20	3	4a	86
6	25	3	4a	87

a) *Reaction condition: isatin; malononitrile; dimedone and Fe_2O_3 was heated at 90 °C for the appropriate time.*



Scheme 1: Synthesis of spirooxindole derivatives.

malononitrile (**2,** 1.0 mmol), different reagents including 1, 3-dicrbonyl compounds, naphthol and 4-hydroxycumarin (**3,** 1.0 mmol) in the present of Fe_2O_3 as an environmentally benign nature catalyst under thermal and solvent-free conditions is reported (scheme 1).

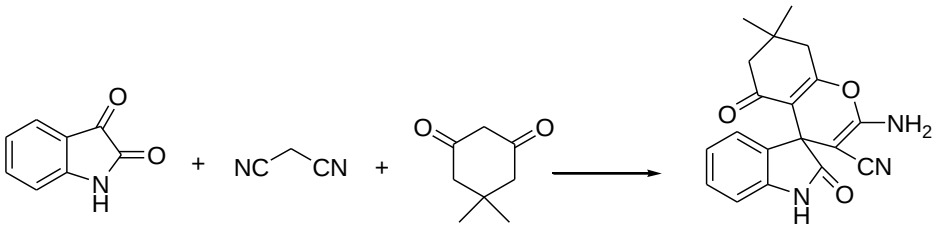
In order to optimized the reaction conditions, the synthesis of compound **4a** was used as a model reaction. The effect of different amount of catalyst on the reaction has been studied in this protocol. No product could be detected in the absence of the catalyst even after 10 h (Table 1, entry 1). The best amount of catalyst was 20 mol % (0.032 g) (Table 1, entry 5). The higher amount of catalyst did not increase the yields products (Table 1, entry 6) and the results are summarized in Table 1.

The effect of temperature was studied by carrying out the model reaction at different temperatures under solvent-free conditions (rt, 40, 60, 80, 90, 110 °C) and the best results were obtained at 90 °C (Table 2, entry 5).

In order to study of this procedure, we have synthesized spiro-*4H*-pyrans (spirooxindole) derivatives in the present of 20 mol % Fe_2O_3 as an efficient catalyst under thermal and solvent-free conditions and the results are shown in Table 3.

After the successful synthesis of spirooxindole derivatives, we turned our attention to the synthesis of spiroacenaphthylene derivatives via acenaphthequinone (**5**, 1.0 mmol), malononitrile (**2**, 1.0 mmol) and different reagents including [1,3-dicrbonyl compounds, naphthol and 4-hydroxycumarin] (**6**, 1.0 mmol) in the present of Fe_2O_3 (Scheme 2) and these compounds have synthesized under similar conditions in excellent yields. The results are shown in Table 4.

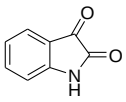
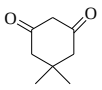
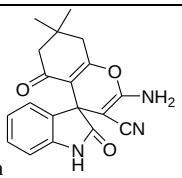
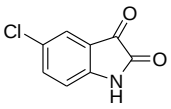
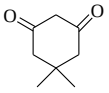
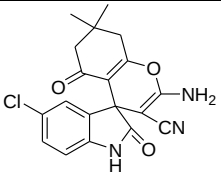
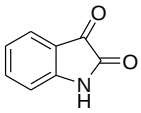
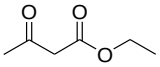
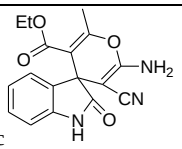
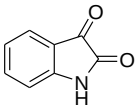
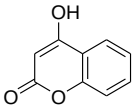
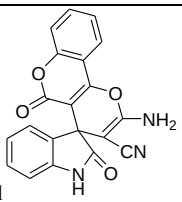
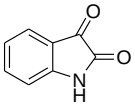
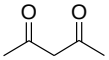
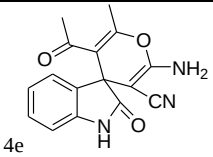
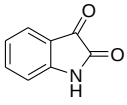
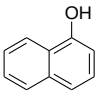
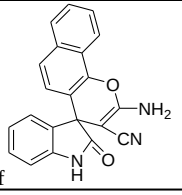
Table 2: Effect of the reaction temperature on the synthesis of 4a [a].



Entry	Temperature (°C)	Time (h)	Isolated Yields (%)
1	r.t.	10	Not product
2	40	8	28
3	60	7	54
4	80	4	71
5	90	3	86
6	110	3	86

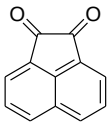
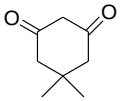
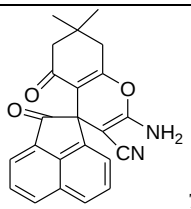
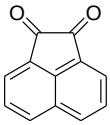
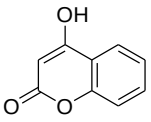
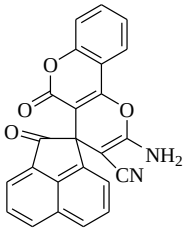
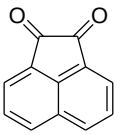
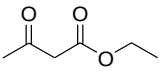
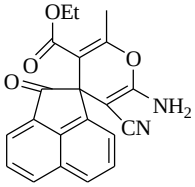
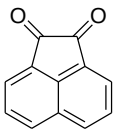
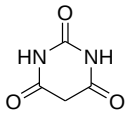
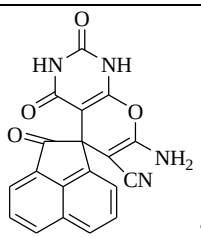
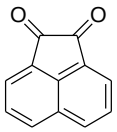
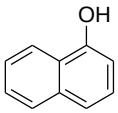
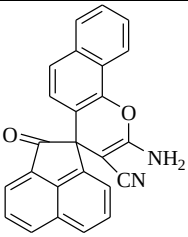
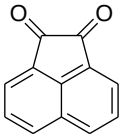
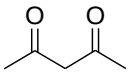
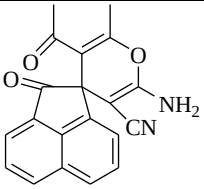
a) Reaction condition: isatin, malononitrile, dimedone (1:1:1) with Fe_2O_3 (20 mol %) was heated under various temperatures for the appropriate time

Table 3: Fe2O3 catalyzed synthesis of spiro-4H-pyrans.

Entry	Isatin	3	Product	Time (h)	Yield % [a]	M.p.˚C	Lit. M.p.˚C
1			 4a	3	86	289-291	290-292 [18]
2			 4b	4	84	283-285	282-284 [27]
3			 4c	6	89	200-202	198-200 [18]
4			 4d	6	81	296-299	298-300 [19]
5			 4e	4	87	239-241	242 [28]
6			 4f	4	83	243-245	242-243 [29]

[a] *Isolated yield*

Table 4: Fe_2O_3 catalyzed synthesis of spiroacenaphthylenes.

Entry	Acenaphthoquinone	7	Product	Time(h)	Yield %[a]	M.p.˚C	Lit. M.p.˚C
1			 7a	4	84	269-271	268-270 [21]
2			 7b	6	81	Mp>300	Mp>300 [21]
3			 7c	5	86	300-302	Mp>300 [21]
4			 7d	5	79	299-302	Mp>300 [21]
5			 7e	4	76	Mp>300	Mp>300 [21]
6			 7f	4	89	Mp>300	Mp>300 [21]

[a] *Isolated yield.*

Comparison of catalytic ability of some catalysts reported in the literature for synthesis of spiro-4*H*-pyran derivatives are shown in Table 5. This study reveals that Fe_2O_3 has shown its extraordinary potential to be a cheap, cost effective, eco-friendly, efficient and environmentally benign nature catalyst for the one-pot synthesis of these heterocyclic compounds, in addition to excellent yields and short reaction times are the notable advantages this methodology.

CONCLUSIONS

In summary, a simple, economical and efficient procedure has been developed for the synthesis of spirooxindole and spiroacenaphthylene derivatives *via* of

Table 5: Comparison of catalytic ability some of catalysts reported in the literature for synthesis of spiro[4H-pyran-oxindoles][a].

Entry	Catalyst	Conditions	Time/Yield (%)	References
1	SSA-MNPs	EtOH/H_2O, 60 °C	80 min/95	[19]
2	Et_3N	EtOH, Reflux	4h/80	[21]
3	β-Cyclodextri	H_2O, 60 °C	5h/90	[24]
4	lipase	H_2O, 30 °C	3h/94	[25]
5	$InCl_3$	MeCN, Reflux	90 min/75	[26]
6	CsF	EtOH, rt	5 min/88	[27]
7	DMAP	microwave	5 min/90	[28]
8	HTM	H_2O, 60 °C	30 min/95	[29]
9	MgO nanocrystalline	H_2O, 80 °C	120 min/95	[30]
10	Fe_2O_3	Solvent-free, 90 °C	3h/86	This work

a) Based on three-component reaction of isatin (1.0mmol), malononitrile (1.0 mmol) and dimedone (1.0 mmol).

one-pot, three-component reaction of isatin/acenaphthequinone (1.0 mmol), malononitrile (1.0 mmol) and different reagents including [1,3-dicrbonyl compounds, naphthol and 4-hydroxycumarin] (1.0 mmol) in the present of Fe_2O_3 as an efficient catalyst under thermal and solvent-free conditions with excellent yields and short reaction times. Simple, mild, high efficiently, environmentally benign, eco-friendly, low-cost, non-toxic catalyst and solvent-free conditions are the most advantages of this method.

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REFERENCES

[1] Ramadoss H., Kiyani H., Mansoor S.S., Triphenylphosphine Catalysed Facile Multicomponent Synthesis of 2-Amino-3-Cyano-6-Methyl-4-Aryl-4H-Pyrans, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **36** (1): 19-26 (2017).

[2] Abaszadeh M., Seifi M., KF/Al_2O_3: As a Solid Phase and Recyclable Basic Catalyst for Synthesis Mono and Bis Pyrimidine Derivatives, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **36** (1): 35-43 (2017).

[3] Keshwal B.S., Rajguru D., Acharya A.D., DBU As A Novel and Highly Efficient Catalyst for The Synthesis of 3,5-Disubstituted-2,6-dicyanoanilines Under Conventional and Microwave Conditions, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **35** (1): 37-42 (2016).

[4] Mohammadi Ziarani G., Aleali F., Lashgari N., Badiei A., An Efficient Green Approach for the Synthesis of Structurally Diversified Spirooxindoles Using Sulfonic Acid Functionalized Nanoporous Silica (SBA-Pr-SO_3H), *Iran. J. Chem. Chem. Eng. (IJCCE)*, **35**(1): 17-23 (2016).

[5] Sarrafi Y., Eghtedari M., Four-Component Reaction between Ethyl Benzoylacetate, Hydroxylamine, Aldehydes and Malononitrile: Synthesis of Isoxazol-5(2H)-Ones, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **35** (2): 9-13 (2016).

[6] Hassanpour A., Hosseinzadeh-Khanmiri R., Ghorbanpour Kh., Abolhasani J., Mosaei Oskoei Y., Synthesis of 3,4-Dihydroquinoxalin-2-Amine, Diazepine-Tetrazole and Benzodiazepine-2-Carboxamide Derivatives with the Aid of $H_6P_2W_{18}O_{62}$/Pyridino-Fe_3O_4, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **35** (4): 39-47 (2016).

[7] Sheikhhosseini E., Sattaei Mokhtari T., Faryabi M., Rafiepour A., Soltaninejad Sh., Iron Ore Pellet, A Natural and Reusable Catalyst for Synthesis of Pyrano[2,3-d]pyrimidine and Dihydropyrano[c]chromene Derivatives in Aqueous Media, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **35** (1): 43-50 (2016).

[8] Mohamadpour F., Maghsoodlou M.T., Heydari R., Lashkari M., Saccharin: a Green, Economical and Efficient Catalyst for the One‐Pot, Multi‐Component Synthesis of 3,4-Dihydropyrimidin-2-(1H)-one Derivatives and 1H‐Pyrazolo[1,2-b]phthalazine-5,10-Dione Derivatives and Substituted Dihydro‐2‐Oxypyrrole, *J. Iran. Chem. Soc*., **13**(8): 1549-1560 (2016).

[9] Al-Hiaza M.A., Mostafa M.S., El-Kady M.Y., synthesis and Biological Evaluation of Some New Coumarin Derivatives, *Molecules*., **8**(2): 275-286 (2003).

[10] Abdel-Rahman A.H., Keshk E.M., Hanna M.A., El-Bady Sh.m., Synthesis and Evaluation of Some New Spiro Indoline-Based Heterocycles as Potentially Active Antimicrobial Agents, *Bioorg. Med. Chem*., **12**(9): 2483-2488 (2004).

[11] Garima Kumari M.M., Rhodium(II) Acetate-Catalyzed Stereoselective Synthesis, SAR and Anti-HIV Activity of Novel Oxindoles Bearing Cyclopropane Ring, *Eur. J. Med. Chem*., **46**(4): 1181–1188 (2011).

[12] Yeung B.K.S., Zou B., Rottmann M., Lakshminarayana S.B., Ang S.H., Leong S.Y., Tan J., Wong J., Keller-Maerki S., Fischli C., Goh A., Schmitt E.K., Krastel P., Francotte E., Kuhen K., Plouffe D., Henson K., Wagner T., Winzeler E.A., Petersen F., Brun R., Dartois V., Diagana T.T., Keller T.H., Spirotetrahydro Beta-Carbolines (spiroindolones): A New Class of Potent and Orally Efficacious Compounds for the Treatment of Malaria, *J. Med. Chem*., **53** (14): 5155–5164 (2010).

[13] Vintonyak V.V., Warburg K., Kruse H., Grimme S., Hübel K., Rauh D., Waldmann H., Identification of Thiazolidinones Spiro-Fused to Indolin-2-ones as Potent and Selective Inhibitors of the Mycobacterium Tuberculosis Protein Tyrosine Phosphatase B, *Angew. Chem. Int. Ed. Engl*., **49**(34): 5902–5905 (2010).

[14] Yu S., Qin D., Shangary S., Chen J., Wang G., Ding K., McEachern D., Qiu S., Nikolovska-Coleska Z., Miller R., Kang S., Yang D., Wang S., Potent and Orally Active Small-Molecule Inhibitors of the MDM2−p53 Interaction, *J. Med. Chem*., **52**(24): 7970–7973 (2009).

[15] Fensome A., Adams W.R., Adams A.L., Berrodin T.J., Cohen J., Huselton C., Illenberger A., Kern J.C., Hudak V.A., Marella M.A., Melenski E.G., McComas C.C., Mugford C.A., Slayden O.D., Yudt M., Zhang Z., Zhang P., Zhu Y., Winneker R.C., Wrobel J.E., Design, Synthesis, and SAR of New Pyrrole-Oxindole Progesterone Receptor Modulators Leading to 5-(7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl) -1-methyl- 1H-pyrrole -2-carbonitrile (WAY-255348), *J. Med. Chem*., **51** (6): 1861-1873 (2008).

[16] Maheshwar Rao B., Niranjan Reddy G., Vijaikumar Reddy T., Prabhavathi Devi B.L.A., Prasad R.B.N., Yadav J.S., Subba Reddy B.V., Carbon–SO_3H: A Novel and Recyclable Solid Acid Catalyst for the Synthesis of Spiro[4H-pyran-3,3′-oxindoles], *Tetrahedron Lett*., **54**(20): 2466-2471 (2013).

[17] Rad-Moghadam K., Youseftabar-Miri L., Ambient Synthesis of Spiro[4H-pyran-oxindole] Derivatives Under [BMIm]BF_4 Catalysis, *Tetrahedron*., **67** (31): 5693-5699 (2011).

[18] Karimi A.R., Sourinia M., Dalirnasab Z., Karimi M., Silica Sulfuric Acid Magnetic Nanoparticle: an Efficient and Ecofriendly Catalyst for Synthesis of Spiro[2-amino-4H-pyran-oxindole]s, *Can. J. Chem*., **93**(5): 546-549 (2015).

[19] Satasia S.P., Kalaria P.N., Avalani J.R., Raval D.K., An efficient approach for the synthesis of spirooxindole derivatives catalyzed by novel sulfated choline based heteropolyanion at room temperature, *Tetrahedron*., **70**(35): 5763-5767 (2014).

[20] Saeedi M., Heravi M.M., Beheshtiha Y.S., Oskooie A., One-pot three-component synthesis of the spiroacenaphthylene derivatives, *Tetrahedron*., **66**(29): 5345-5348 (2010).

[21] Li Y., Chen H., Shi D., Ji S., Efficient One-Pot Synthesis of Spirooxindole Derivatives Catalyzed by l-Proline in Aqueous Medium, *J. Comb.Chem*., **12**(2): 231-238 (2010).

[22] Hari G.S., Lee Y.R., Efficient One-Pot Synthesis of Spirooxindole Derivatives by Ethylenediamine Diacetate Catalyzed Reactions in Water, *Synthesis*., **3**: 453-464 (2010).

[23] Sridhar R., Srinivas B., Madhav B. , Reddy V.P. , Nageswar Y.V.D., Rao K.R., Multi-Component Supramolecular Synthesis of Spirooxindoles Catalyzed by β-Cyclodextrin in Water, *Can. J. Chem*., **87** (12): 1704-1707 (2009).

[24] Chai S.J., Lai Y.F., Xu J.C., Zheng H., Zhu Q., Zhang P.F., One-Pot Synthesis of Spirooxindole Derivatives Catalyzed by Lipase in the Presence of Water, *Adv. Synth. Catal*., **353**(2-3): 371-375 (2011).

[25] Shanthi G., Subbulakshmi G., Perumal P.T., A New $InCl_3$-Catalyzed, Facile and Efficient Method for the Synthesis of Spirooxindoles under Conventional and Solvent-Free Microwave Conditions, *Tetrahedron*., **63** (9): 2057-2063 (2007).

[26] Wagh Y.B., Tayade Y.A., Padvi S.A., Patil B.S., Patil N.B., Dalal D.S., A Cesium Fluoride Promoted Efficient and Rapid Multicomponent Synthesis of Functionalized 2-Amino-3-Cyano-4H-Pyran and Spirooxindole Derivatives, *Chin. Chem. Lett*., **26** (10): 1273-1277 (2015).

[27] Zakeri M., Nasef M.M., Abouzari-Lotf E., Moharami A., Heravi M.M., Sustainable Alternative Protocols for the Multicomponent Synthesis of Spiro-4H-pyrans catalyzed by 4-Dimethylaminopyridine, *J. Ind. Eng. Chem*., **29** (1): 273-281 (2015).

[28] Wang G.-D., Zhang X.-N., Zhang Z.-H., One-Pot Three-Component Synthesis of Spirooxindoles Catalyzed by Hexamethylenetetramine in Water *J. Heterocyclic. Chem*., **50**(1): 61-65 (2013).

[29] Karmakar B., Nayak A., Banerji J., A Clean and Expedient Synthesis of Spirooxindoles in Aqueous Media Catalyzed over Nanocrystalline MgO, *Tetrahedron Lett*., **53**(37): 5004-5007 (2012).