

## Green Chemistry Approach for Efficient Synthesis of Some New Spiro [Indoline-3,4'-Pyran] Derivatives and Prediction their Biological Activity by PASS INET

Fathy F. Abdel-latif<sup>1,\*</sup>, Mohamed A. Ameen<sup>1</sup>, Omar M. Elhady<sup>2</sup> and Moumen S. Kamel<sup>1</sup>.

<sup>1</sup>Chemistry Department, Faculty of Science, Minia University, El Minia 61511, Egypt.

<sup>2</sup>Chemistry Department, Faculty of Science, Sohag University, Sohag 82524, Egypt.

Received: 5 May 2015, Revised: 6 Jun. 2015, Accepted: 7 Jun. 2015.

Published online: 1 Sep. 2015.

**Abstract:** Some new spiro compounds have been synthesized by reaction of isatin with different nucleophiles containing activemethylene compounds. Their chemical structures have been confirmed by IR, <sup>1</sup>HNMR and by elemental analysis.

**Keywords:** One pot synthesis, Diammonium hydrogen phosphate, Isatin, Aqueous media, MW, PASS Inet.

### 1 Introduction

In recent years, it has been recognized that conditions for chemical reactions have to be modified in order to reduce waste and to minimize harmful organic solvents [1]. Alternatives to meet these conditions include carrying out organic reactions in water, supercritical gases [2] or solvent-free conditions [3, 4].

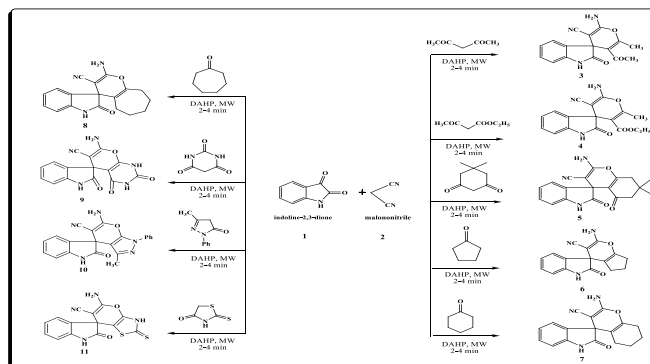
Indeed, water is well known as an attractive solvent medium for many organic reactions because it is the cheapest and most abundantly available solvent. Reactions in aqueous media are generally environmentally safe, devoid of any carcinogenic effects, simple work up, comparatively cheaper to operate, and especially important in industry.

The 4H-Pyran nucleus is a fertile source of biologically important molecules possessing a wide spectrum of biological and pharmacological activities, such as antimicrobial [5], antiviral [6,7], mutagenicity [8], antiproliferative [9], sex pheromone [10], antitumor [11], cancer therapy [12-14] and central nervous system activity [15]. Some of these compounds are widely employed as cosmetics and pigments and as potential biodegradable agrochemicals [16]. Therefore, the synthesis of such compounds has attracted strong interest by us and others. In last paper we focused on the preparation of 4H-pyran

derivatives 4 in aqueous media using DAHP as a catalyst [17].

### 2 Results and Discussion

Many of 4H-pyran or isatine derivatives have been synthesized by us as one of our interesting area of research [18-21] but the synthesized spiro derivatives bearing both moieties have not been reported yet. Therefore, our aim was to prepare these new spiro compounds at C-3 carbon of isatine 3 – 11 by the reaction of isatine with malononitrile and different nucleophiles in one-pot rapid and efficient procedure. The spiro isatinpyran systems were prepared by catalytic amount of DAHP in a aqueous condition under the influence of MW irradiations (Scheme 1).



Scheme 1. The synthesis of compounds 3-11

\* Corresponding author E-mail: fathyfahim53@yahoo.com

In this work these spiro compounds were made by one-pot procedure in short time without isolation of any intermediate and the reaction yields increased.

In the case of isatin the reaction rate was increased because the C=O group in 2 position of isatin increases the reactivity of carbon in 3 position by electron-withdrawing effect.

All prepared spiro compounds were purified by filtration and recrystallization of crude products from ethanol/water (70/30) solution (Scheme 1). The structures of compounds **3-11** were deduced from their elemental analyses and their IR, <sup>1</sup>H NMR and Mass spectroscopic measurements. All compounds have shown an excellent agreement between calculated and experimentally obtained data for CHN analysis. For example the <sup>1</sup>H NMR spectrum of **3** exhibited broad singlet at 10.39 ppm readily recognized to arise from NH-isatin with multiplets (δ7.00-7.50) for the aromatic protons. The singlet at 7.13 ppm is related to NH<sub>2</sub>.

### 3 Biological activity

#### 3.1 Biological activity predicted by PASS

The biological activity spectra for all nine synthesized compounds (**3-11**) were obtained by PASS software [22-23]. The predictions of biological activity by using PASS software were carried out based on analysis of training set containing about 46,000 drugs and biologically active compounds. This set consider as reference compounds for known chemical compounds as well as different biological activities. The percent activity (Pa) and inactivity (Pi) of our products are summarized in table 1. We have also selected the types of activities, which show high biological activity predicted for a potential compound with the highest probability. According to these data the most frequently predicted types of biological activities are Oxidoreductase inhibitor,

Chemosensitizer, Potassium channel large-conductance Ca-activated activator, Cystinyl aminopeptidase inhibitor and Neurotransmitter uptake inhibitor. We can pointed out that in compound **4** such activity as Oxidoreductase inhibitor has also been predicted, as well as in compound **6**, **7**, **8** such activity as Cystinyl aminopeptidase inhibitor and Potassium channel large-conductance Ca-activated activator, compound **10** such activity as Nicotinic acid receptor 1 agonist with percentage 86% has also been predicted.

### 4 Experimental

Mps determined using open glass capillaries on a gallenkamp melting point apparatus and were uncorrected. The IR spectra were recorded a Shimaduz 408 instrument using potassium bromide pellets. The <sup>1</sup>H NMR (400 MHz) spectra were measured in DMSO-d<sub>6</sub> using a Burker AM 400 with TMS as an internal standard.

#### 4.1 Synthesis of the title products (general procedures)

A solution of isatin **1** (1 mmol), malononitrile **2** (1 mmol), nucleophile (1 mmol), and DAHP (13.2 mg, 10 mol %) in H<sub>2</sub>O

(10 mL) and EtOH (5 mL) was mixed in a beaker and subjected to M.W at 900 W (20% power) for 2-4 minutes. After the completion of the reaction, the solid product was collected by filtration and purified by washing with aqueous ethanol.

The characterization of the title products are listed below (compounds **3**, **4**, **6**, **7**, **8** and **10** were reported [24]).

**Table 1:** Predicted activity of synthesized compounds.

Compounds	Potassium channel large-conductance Ca-activated activator		Cystinyl aminopeptidase inhibitor		Oxidoreductase inhibitor		Chemosensitizer		Neurotransmitter uptake inhibitor	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
<b>3</b>	0.569	0.003	0.481	0.005	0.448	0.003	0.481	0.005	0.394	0.118
<b>4</b>	0.479	0.003	0.545	0.04	0.625	0.003	0.545	0.04	0.332	0.173
<b>5</b>	0.563	0.003	0.553	0.004	0.408	0.003	0.553	0.004	0.573	0.019
<b>6</b>	0.636	0.002	0.648	0.003	0.491	0.002	0.648	0.003	0.599	0.036
<b>7</b>	0.636	0.002	0.648	0.003	0.491	0.002	0.648	0.003	0.599	0.036
<b>8</b>	0.636	0.002	0.648	0.003	0.491	0.002	0.648	0.003	0.599	0.036
<b>9</b>	0.508	0.003	0.454	0.005	0.378	0.003	0.454	0.005	0.392	0.119
<b>10</b>	0.463	0.003	0.387	0.008	0.46	0.003	0.387	0.008	0.340	0.164
<b>11</b>	0.524	0.003	0.471	0.005	0.372	0.003	0.471	0.005	0.459	0.079

3'-Acetyl-6'-amino-2'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile (**3**): Yellow powder; Yield 80%, m.p.: 270-275 °C ; IR (KBr,  $\text{Cm}^{-1}$ ): 3369, 3295 and 3195( $\text{NH}_2$ , NH); 2193 (CN), 1716, 1661(CO).  $^1\text{H-NMR}$

(400 MHz, DMSO,  $\text{d}_6$ ):  $\delta$  2.09 (s, 3H,  $\text{CH}_3$ -pyran), 2.29 (s, 3H,  $\text{CH}_3$ -acetyl), 6.79 (d, 1H, CH-Ar), 6.93 (t, 1H, CH-Ar), 6.99 (d, 1H, CH-Ar), 7.13 (s, 2H,  $\text{NH}_2$ ), 7.19 (t, 1H, CH-Ar), 10.39 (s, 1H, NH).

2'-Amino-6'-methyl-2-oxo-5'-propionylspiro[indoline-3,4'-pyran]-3'-carbonitrile (**4**): Yellow powder; Yield 80%, m.p.: 268-270 °C; IR (KBr,  $\text{Cm}^{-1}$ ): 3465, 3369 and 3260 ( $\text{NH}_2$ , NH), 2189 (CN), 1723, 1680 (CO).  $^1\text{H-NMR}$  (400 MHz, DMSO,  $\text{d}_6$ ):  $\delta$  0.78 (t, 3H,  $\text{CH}_3$ -ester), 3.16 (s, 3H,  $\text{CH}_3$ -pyran), 3.76 (q, 2H,  $\text{CH}_2$ -ester), 6.82 (d, 1H, CH-Ar), 6.95 (t, 1H, CH-Ar), 6.99 (d, 1H, CH-Ar), 7.13 (s, 2H,  $\text{NH}_2$ ), 7.20 (t, 1H, CH-Ar), 10.39 (s, 1H, NH).

2-Amino-7,7-dimethyl-5-methylene-2'-oxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (**5**): Yellow powder; Yield 91%, m.p.: > 300 °C; IR (KBr,  $\text{Cm}^{-1}$ ): 3369, 3295 and 3195 ( $\text{NH}_2$ , NH) , 2194 (CN), 1717, 1673 (CO).  $^1\text{H-NMR}$  (400 MHz, DMSO,  $\text{d}_6$ ):  $\delta$  1.04 (s, 6H, 2 $\text{CH}_3$ ), 2.12 (s, 2H,  $\text{CH}_2$ ), 2.57 (s, 2H,  $\text{CH}_2$ ), 6.82 (d, 1H, CH-Ar), 6.95 (t, 1H, CH-Ar), 6.99 (d, 1H, CH-Ar), 7.13 (s, 2H,  $\text{NH}_2$ ), 7.20 (t, 1H, CH-Ar), 10.39 (s, 1H, NH).

2-Amino-2'-oxo-6,7-dihydro-5H-spiro[cyclopenta[b]pyran-4,3'-indoline]-3-carbonitrile (**6**): Yellow powder; Yield 86%, m.p.: 240-242 °C; IR (KBr,  $\text{Cm}^{-1}$ ): 3451, 3348 and 3270 ( $\text{NH}_2$ , NH), 2199 (CN), 1724 (CO).  $^1\text{H-NMR}$  (400 MHz, DMSO,  $\text{d}_6$ ):  $\delta$  1.08 (t, 2H,  $\text{CH}_2$ ), 1.92 (m, 2H,  $\text{CH}_2$ ), 2.17 (t, 1H, CH), 2.56 (t, 1H, CH), 6.99 (d, 1H, CH-Ar), 7.11 (t, 1H, CH-Ar), 7.30 (d, 1H, CH-Ar), 7.40 (t, 1H, CH-Ar), 7.95 (s, 2H,  $\text{NH}_2$ ), 11.30 (s, 1H, NH).

2-Amino-2'-oxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (**7**): Yellow powder; Yield 83%, m.p.: 256-260 °C; IR (KBr,  $\text{Cm}^{-1}$ ): 3460, 3366 and 3291 ( $\text{NH}_2$ , NH), 2210 (CN), 1732 (CO).  $^1\text{H-NMR}$  (400 MHz, DMSO,  $\text{d}_6$ ):  $\delta$  1.66 (m, 4H, 2 $\text{CH}_2$ ), 1.92 (t, 2H,  $\text{CH}_2$ ), 2.23 (t, 2H,  $\text{CH}_2$ ), 6.98 (d, 1H, CH-Ar), 7.09 (t, 1H, CH-Ar), 7.23 (d, 1H, CH-Ar), 7.37 (t, 1H, CH-Ar), 7.76 (s, 2H,  $\text{NH}_2$ ), 11.30 (s, 1H, NH).

2-amino-2'-oxo-6,7,8,9-tetrahydro-5H-spiro[cyclohepta[b]pyran-4,3'-indoline]-3-carbonitrile (**8**): Yellow powder; Yield 81%, m.p.: 242-246 °C; IR (KBr,  $\text{Cm}^{-1}$ ): 3451, 3325 and 3219 ( $\text{NH}_2$ , NH), 2212 (CN), 1734 (CO).  $^1\text{H-NMR}$  (400 MHz, DMSO,  $\text{d}_6$ ):  $\delta$  1.09 (t, 1H,  $\text{CH}_2$ ), 1.94 (m, 6H, 3 $\text{CH}_2$ ), 2.07 (t, 2H,  $\text{CH}_2$ ), 2.81 (t, 1H,  $\text{CH}_2$ ), 7.06 (d, 1H, CH-Ar), 7.20 (t, 1H, CH-Ar), 7.40 (d, 1H, CH-Ar), 7.73 (t, 1H, CH-Ar), 7.83 (s, 2H,  $\text{NH}_2$ ), 11.27 (s, 1H, NH).

7'-Amino-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-6'-carbonitrile (**9**): Yellow powder; Yield 79%, m.p.: 280-285 °C; IR (KBr, $\text{Cm}^{-1}$ ): 3375, 3262 and 3173 ( $\text{NH}_2$ , NH), 2204 (CN), 1701 (CO).

$^1\text{H-NMR}$  (400 MHz, DMSO,  $\text{d}_6$ ):  $\delta$  6.79-7.19 (m, 6H, CH-Ar,  $\text{NH}_2$ ), 10.48 (s, 1H, NH), 11.11 (s, 1H, NH), 12.76 (s, 1H, NH).

6'-Amino-3'-methyl-2-oxo-1'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (**10**): Light pink powder; Yield 80%, m.p.: 255-258 °C; IR (KBr,  $\text{Cm}^{-1}$ ): 3411, 3330 and 3270 ( $\text{NH}_2$ , NH), 2193 (CN), 1716 (CO).  $^1\text{H-NMR}$  (400 MHz, DMSO,  $\text{d}_6$ ):  $\delta$  1.15 (s, 3H,  $\text{CH}_3$ ), 6.99-7.79 (m, 9H, CH-Ar), 7.81 (s, 2H,  $\text{NH}_2$ ), 10.74 (s, 1H, NH).

5'-Amino-2-oxo-2'-thioxo-2',3'-dihydrospiro[indoline-3,7'-pyrano[2,3-d]thiazole]-6'-carbonitrile (**11**): Black powder; Yield 84%, m.p.: >300 °C; IR (KBr,  $\text{Cm}^{-1}$ ): 3560, 3426 and 3342 ( $\text{NH}_2$ , NH), 2265 (CN), 1687 (CO).  $^1\text{H-NMR}$  (400 MHz, DMSO,  $\text{d}_6$ ):  $\delta$  6.92-7.41 (m, 4H, CH-Ar), 8.76 (s, 2H,  $\text{NH}_2$ ), 11.20 (s, 1H, NH), 14.00 (s, 1H, NH).

## References

- [1] J. A. Linthorst, An overview: origins and development of green chemistry, *Found Chem*, 12:55–68 (2010).
- [2] J. A. Linthorst, Nediljko Budisa and Dirk Schulze-Makuch, Supercritical Carbon Dioxide and Its Potential as a Life-Sustaining Solvent in a Planetary Environment, *Life*, **4**, 331-340 (2014).
- [3] Martins MAP, Frizzo CP, Moreira DN et al. Solvent-free heterocyclic synthesis. *Chem. Rev.* 109, 4140 – 4182 (2009).
- [4] Ahmed M. M. El-Saghier, Eman A. Ahmed and Ahmed M. A. Mahmoud, *J. Pharm. Appl. Chem.*, 1, 9-19 (2015).
- [5] M.M. Khafagy, A.H.F.A. El-Wahas, F.A. Eid El-Agrody, Synthesis of halogen derivatives of benzo[h]chromene and benzo[a]anthracene with promising antimicrobial activities. *A.M. Farmaco*. 57, 715(2002).
- [6] W.P. Smith, L.S. Sollis, D.P. Howes, C.P. Cherry, D.I. Starkey, N.K. Cobley, H. Weston, J. Scicinski, A. Merritt, A. Whittington, P. Wyatt, N. Taylor, D. Green, R. Bethell, S. Madar, R.J. Fenton, P.J. Morley, T. Pateman. Dihydropyranocarboxamides Related to Zanamivir: A New Series of Inhibitors of Influenza Virus Sialidases. 1. Discovery, Synthesis, Biological Activity, and Structure–Activity Relationships of 4-Guanidino- and 4-Amino-4H-pyran-6-carboxamides, Dihydropyranocarboxamides Related to Zanamivir. *A. J. Beresford Med. Chem.*, 41, 787 (1998).
- [7] A. G. Martinez, L. J. Marco, Friedlander reaction on 2-amino-3-cyano-4H-pyrans, synthesis of derivatives of 4H-pyran[2,3-b]quinoline, new tacrine analogues. *Bioorg. Med. Chem. Lett.* 7, 3165–3170(1997).
- [8] K. Hirmoto, A. Nasuhara, K. Michiloshi, T. Kato, K. Kikugawa, DNA strand-breaking activity and mutagenicity of 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one (DDMP). A Maillard reaction product of glucose and glycine. *Mutation Res.* 395, 47–56(1997).
- [9] C. P. Dell, C. W. Smith, Antiproliferative derivatives of 4H-naphtho [1, 2-b] pyran and process for their preparation. *Eur.*

- Pat. 537, 94, 9 21 Apr 1993; ref. *Chem. Abstr.* 119, 139102d (1993).
- [10] G. Bianchi, A. Tava Agric, Synthesis of (2R)-(+)-2, 3-Dihydro-2, 6-dimethyl-4H-pyran-4-one, a Homologue of Pheromones of a Species in the Hepialidae Family. *Biol. Chem.*, 51, 2001(1987).
- [11] S.J. Mohr, M.A. Chirigos, F.S. Fuhrman, J.W., Pyran copolymer as an effective adjuvant to chemotherapy against a murine leukemia and solid tumor. *Pror Cancer Res.*, 35, 3750(1975).
- [12] Skommer J, Wlodkowic D, Matto M, Eray M, Pelkonen J. HA14-1, a small molecule Bcl-2 antagonist, induces apoptosis and modulates action of selected anticancer drugs in follicular lymphoma B cells. *Leuk Res.* 30, 322–331(2006).
- [13] D.R. Anderson, S. Hegde, E. Reinhard, L. Gomez, W.F. Vernier, L. Lee, S. Liu, A. Sambandam, P.A. Snider, L. Masih, Aminocyanopyridine inhibitors of mitogen activated protein kinase-activated protein kinase 2 (MK-2). *Bioorg. Med. Chem. Lett.*, 15, 1587-1590(2005).
- [14] J.L. Wang, D. Liu, Z. Zhang, S. Shan, X. Han, S.M. Srinvasula, C.M. Croce, E.S. Alnemer, Z. Huang Proc, Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells . *Natl. Acad. Sci. USA*, 97, 7124-7129(2000).
- [15] F. Eiden, F. Denk, Synthesis and CNS activity of pyrane derivatives: 6, 8-dioxabicyclo (3, 2, 1)-octanes, *Arch. Pharm. Weinheim Ger.* 324, 353–354(1991).
- [16] E.A.A. Hafez, M.H. Elnagdi, A.G.A. Elagamey, F.M.A.A. El-Taweel, "Nitriles in heterocyclic synthesis: novel synthesis of benzo[c]-coumarin and of benzo[c]pyrano[3,2-c]quinoline derivatives," *Heterocycles*. 26, 903-907(1987).
- [17] M.A. Ameen, S.M. Motamed, F.F. Abdel-latif, Highly efficient one-pot synthesis of dihydropyran heterocycle . *Chinese Chemical Letters*, 25, 212–214(2014).
- [18] F.F. Abdel-latif, R. M. Shaker. *Bull Soc Chim Fr.* 127, 87(1991).
- [19] F.F. Abdel-latif, R. M. Shaker, N. S. Abdel-Aziz. *Heterocycl. Commun.* 3, 245(1997).
- [20] R. M. Shaker, A.F. Mahmoud, F.F. Abdel-latif., *Phosphorous, Sulfur and silicon*, 160, 207(2000).
- [21] R. M. Shaker, F.F. Abdel-latif. *J. Chem. Res. (S)*, 294(1997).
- [22] <http://www.ibmc.msk.ru/PASS/>.
- [23] V. V. Poroikov and D. A. Filimonov, "PASS: prediction of biological activity spectra for substances," in *Predictive Toxicology*, C. Helma, Ed., pp. 459–478(2005), Taylor & Francis, London, UK,.
- [24] M. A. A. Mohammed, MSc Synthesis of Some New Spiro Heterocyclic Systems, Faculty of Science at Sohag, South Valley University (1996).