Research Article

Open Access

Fazilat Ayambekam and Majid Ghashang*

Preparation of skeletally diverse quinazoline-2,4(1H,3H)-diones using $\text{Na}_2\text{SiO}_3/\text{SnFe}_2\text{O}_4$ catalytic system through a four-component reaction

<https://doi.org/10.1515/mgmc-2020-0008>

Received December 13, 2019; accepted April 23, 2020.

Abstract: Sodium silicate with the formula of Na_2SiO_3 was used for the four-component reaction of ketones, aldehydes and cyanoacetamide. The effect of SnFe_2O_4 nano-particles on the catalytic potential of Na_2SiO_3 was investigated. The desired products synthesized by this method are 5-amino-7-aryl-2,4-dioxo-2,3,4,4a,7,7a,8,9,10,11-decahydro-1H-benzo[i]quinazoline-6-carbonitriles, 5-amino-2,4-dioxo-7-aryl-1,2,3,4,4a,7,7a,8,10,11-decahydropyrano[3,4-i]quinazoline-6-carbonitrile, 5-amino-9-methyl-2,4-dioxo-7-aryl-2,3,4,4a,7,7a,8,9,10,11-decahydro-1H-pyrido[3,4-i]quinazoline-6-carbonitrile and 5-amino-2,4-dioxo-7-aryl-1,2,3,4,4a,7,7a,8,10,11-decahydrothiopyrano[3,4-i]quinazoline-6-carbonitrile derivatives. This method has advantages of high yields, simple procedure and easy work-up.

Keywords: quinazoline-2,4(1H,3H)-diones; Na_2SiO_3 ; SnFe_2O_4 nano-particles; benzo[i]quinazoline; pyrano[3,4-i]quinazoline; thiopyrano[3,4-i]quinazoline

1 Introduction

Heterocycles bearing quinazoline core structures played a significant role in research fields such as chemistry, drug development and biological investigations (Ghashang, 2012; Ghashang et al., 2013, 2015). Quinazoline and especially quinazoline-2,4(1H,3H)-dione derivatives have

attracted significant attention due to diverse pharmacological activities such as anti-proliferative activities against HCT-116 and MCF-7 cell lines (Hei et al., 2016), anti-proliferative activity in LNCaP and prostate cancer cell lines (Maestri et al., 2017), isoform-selective PI3K- α inhibition (Yadav et al., 2016), PARP-1/2 inhibition activity (Zhou et al., 2018).

Quinazoline-2,4(1H,3H)-dione moiety could be constructed by cyclization of 2-aminobenzonitrile with DMF (Rasal and Yadav, 2016), the reaction of CO_2 and 2-aminobenzonitriles (Ma et al., 2013), carbonylation and then cyclization of anthranilamide (Li, 2009), and treatment of substituted anthranilic acid with potassium cyanate (El-Brollosy, 2007). However, quinazoline-2,4(1H,3H)-diones can be synthesized via many methods but most of them suffer from structure diversity and scope expanding. A new method for the preparation of important scaffolds with a core of quinazoline-2,4(1H,3H)-dione has been developed by Jiang et al. through a multicomponent reaction of aldehydes, cycloketones, and cyanoacetamide under MW irradiation conditions using K_2CO_3 and Cs_2CO_3 as basic catalysts (Jiang et al., 2009, 2016).

Sodium silicate with a general formula of $\text{SiO}_2(\text{Na}_2\text{O})_n$ is a white powder that dissolves easily in water and provides an alkaline solution which is stable in neutral and alkaline media. Depending on their prepared ways and purity, sodium silicate has a unique chemistry and has own industrial and consumer applications. One of the important uses of sodium silicate is its use in the manufacture of detergents and ceramic and tile industries. The participation of sodium silicate in the composition of detergents will control the corrosion and alkaline attack. It also acts as a melting aid and prevents cracking of biscuits (Ebnesajjad, 2011; Lagaly et al., 2005). The use of sodium silicate increased stiffness and reduced permeability in predominantly granular soils. Impregnation of concrete with sodium silicate reduces porosity and increases its longevity. Sodium silicates are known to reduce lead, copper and other heavy metals in

* Corresponding author: Majid Ghashang, Department of Chemistry, Najafabad Branch, Islamic Azad University, Najafabad, Iran; P.O. Box: 517, tel: +98-3142291111, fax: +98-3142291016
e-mail: ghashangmajid@gmail.com, ghashangmajid@pmt.iaun.ac.ir
Fazilat Ayambekam, Department of Chemistry, Najafabad Branch, Islamic Azad University, Najafabad, Iran; P.O. Box: 517, tel: +98-3142291111, fax: +98-3142291016

drinking water and reduce the calcium and magnesium hardness (Ebnesajjad, 2011; Lagaly et al., 2005). Their function is used as a corrosion inhibitor to form a microscopic film on the inside of the water pipe and to prevent the formation of bells. Silicates are used to remove oil, wax, and soot from cotton in the weaving industry. In agriculture, soluble silicates are a vital nutrient for plant health and, in small quantities, increase plant resistance to disease and increase yields. The use of sodium silicate reduces the friction resistance to 5%, which results in less fuel consumption for trucks and trucks (Ebnesajjad, 2011; Lagaly et al., 2005).

Sodium silicate has been used for the acceleration of numerous organic transformations such as biodiesel production (Guo et al., 2010), production of lactic acid from rapeseed oil (Long et al., 2011), transesterification of soybean oil to biodiesel (Guo et al., 2012), transesterification of waste cooking oil to biodiesel (Daramola et al., 2015), preparation of Pyrano [2,3-d] pyrimidine derivatives (Abaszadeh et al., 2019), synthesis of pyrano[2,3-d] pyrimidines (Sheikhan-Shamsabadi and Ghashang, 2017), preparation of 2-amino-5-oxo-4-aryl-4,5-dihydroindeno[1,2-b] pyran-3-carbonitriles (Fazlinia and Sheikh, 2018), preparation of Pyrido[2,3-b]indoles (Sheikh and Fazlinia, 2018).

In this, we aim to investigate the effect of SnFe_2O_4 nano-particles on the catalytic activity of Na_2SiO_3 and to prepare a series of quinazoline-2,4(1H,3H)-dione through a multi-component reaction of aldehydes, cycloketones, and cyanoacetamide under solvent-free conditions using a mixture of $\text{SnFe}_2\text{O}_4/\text{Na}_2\text{SiO}_3$ (Scheme 1).

2 Results and discussion

X-ray diffraction patterns (XRD) of pure SnFe_2O_4 nanoparticles and sodium silicate combined with different ratios of SnFe_2O_4 nanoparticles are shown in Figure 1. Accordingly, SnFe_2O_4 nanoparticles have amorphous particles.

Figure 1 also shows the XRD pattern of sodium silicate/ SnFe_2O_4 samples which are prepared through the combination of sodium silicate in solution form with SnFe_2O_4 nanoparticles with a ratio of 0.5, 1, and 2% w/w. In all of the patterns sodium Silicate with the formula of Na_2SiO_3 shows hexagonal structure (Ref. code: 00-016-0818) with the characteristic peaks of 16.8, 24.9, 29.3, 34.8, 37.2, 45.5, 48.1, 49.4, 52.0, 64.1, and 65.7 [$2\theta^\circ$].

The morphology of the synthesized nanoparticles was studied through the FESEM test (Figure 2). Observations show that homogeneous spherical nano-particles of SnFe_2O_4 with dimensions of less than 50 nm were formed. The images taken from mixed samples indicate the formation of almost homogeneous samples in which SnFe_2O_4 nanoparticles are distributed homogeneously in the sodium silicate structure.

First the preparation of 5-amino-2,4-dioxo-7-phenyl-2,3,4,4a,7,7a,8,9,10,11-decahydro-1H-benzo[i]quinazoline-6-carbonitrile (**1d**) through the four-component reaction of cyanoacetamide, cyclohexanone, and benzaldehyde using NaOH and Na_2SiO_3 as basic catalysts under solvent-free conditions (100°C) was investigated (Table 1). Na_2SiO_3 shows a higher yield (Table 1, entry 2). By increasing the temperature to 130°C , the product yield was increased up to 75% (Table 1, entry 3). Subsequently, SnFe_2O_4 nano-particles were added to sodium silicate with three different ratios as 0.5, 1, and 2% w/w. The catalytic activity of three samples was examined under solvent and solvent-free conditions and the results are summarized in Table 1 (entries 4-11). The results show that solvent suppressed the reaction process and all solvent media are inferior and no product yield was formed. Notably, the addition of SnFe_2O_4 nano-particles increased the productivity of Na_2SiO_3 in solvent-free conditions. The higher yield was achieved when sampling with 2% w/w of SnFe_2O_4 nano-particles was used. Finally, Na_2SiO_3 containing 2% w/w of SnFe_2O_4 was selected as the most effective catalyst for the preparation of **1d**.

The effect of catalyst dosage on the product yield is shown in Table 1. Accordingly, the reaction of cyanoacetamide, cyclohexanone and benzaldehyde was

Scheme 1: Four-component reaction of aldehydes, cycloketones, and cyanoacetamide.

Figure 1: XRD patterns of pure SnFe_2O_4 nanoparticles and sodium silicate/ SnFe_2O_4 mixture with a ratio of 0.5, 1, and 2% w/w of SnFe_2O_4 /sodium silicate.

Figure 2: FE-SEM images of Zn_2SnO_4 nanoparticles (a) and sodium silicate/ SnFe_2O_4 mixture with a ratio of 0.5% w/w (b), 1% w/w (c), and 2% w/w (d) of SnFe_2O_4 .

investigated at 130°C in the presence of different amounts of catalyst (Na_2SiO_3 (with 2% of SnFe_2O_4)). The results show that 7.1% mol of the catalyst has the highest efficiency to produce a high yield of product **1d**. No notable increase was done on the product yield with increasing the catalyst dosages to higher than 7.1% mol.

Temperature is one of the effective parameters on the productivity of multi-component reactions. Thus the reaction of cyanoacetamide, cyclohexanone, and benzaldehyde in the was investigated at different temperatures (Table 1). Giving access to **1d** as the expected product is not effective at below 100°C. The reaction has a reasonable high yield at 130°C and no notable change in reaction yield was observed with further increasing of the reaction temperature. Finally, the optimum condition for the preparation of **1d** was chosen as Na_2SiO_3 with 2% w/w of SnFe_2O_4 as catalyst (7.1% mol), temperature (130°C) and solvent-free condition.

Under the above-optimized conditions, the scope of the work was examined using various aromatic aldehydes substituted with different electron-donating and electron-withdrawing groups. The results are shown in Table 2. In all cases a series of 5-amino-2,4-dioxo-7-aryl-2,3,4,4a,7,7a,8,9,10,11-decahydro-1H-benzo[i]quinazoline-6-carbonitriles were synthesized in high yields (Table 2, entries **1d-5d**). The procedure is flexible for structural

modifications. In continue, the scope of the work was expanded using different cyclic ketones including cyclopentanone and tetrahydro-4H-thiopyran-4-one led to the synthesis of products **1e-7e**, **1f-7f**, and **1g-3g**, respectively (Table 2).

Next, the reaction conditions were further modified and the reactions were performed under ultrasonic radiation conditions and high speed ball milling (HSBM) technique. In all reaction conditions, high yield products were obtained. Generally, aromatic aldehydes substituted at *para* and *meta* positions with halogen atoms show more reactivity compared to those of electron-donating groups (e.g. CH_3 , OCH_3). *ortho*-Substituted aldehydes showed longer reaction times than their *para*-counterparts.

The proposed mechanism responds that the initiation of the reaction will include the Knoevenagel condensation reaction of cyanoacetamide with benzaldehyde and cyclohexanone to form 2-cyano-3-phenylacrylamide (**1**) and 2-cyano-2-cyclohexylideneacetamide (**2**) intermediates which can be catalyzed by Na_2SiO_3 . Compound **2** reacts with a base to form an anion intermediate which subsequently undergoes a nucleophilic 1,4-addition to form **3**. The next steps consisted of cyclization, intramolecular reactions, and finally 1,3-H shift to form the desired products (Scheme 2).

Table 1: Preparation of **1d**: catalyst and solvent screening, effect of catalyst dosage and temperature.

Entry	Catalyst	Solvent (20 mL)	t (°C)	Time (h)	Yield (%)
1	NaOH (8.7% mol)	-	100	5	30
2	Na_2SiO_3 (8.7% mol)	-	100	5	35
3	Na_2SiO_3 (8.7% mol)	-	130	5	75
4	A (7.1% mol)	-	130	3	73
5	B (7.1% mol)	-	130	3	72
6	C (7.1% mol)	-	130	3	91
7	C (7.1% mol)	EtOH	Reflux	3	-
8	C (7.1% mol)	DMF	Reflux	3	-
9	C (7.1% mol)	CH_3CN	Reflux	3	-
10	C (7.1% mol)	Toluene	Reflux	3	-
11	C (7.1% mol)	Ethylene glycol	130	3	-
12	C (7.1% mol)	-	120	3	80
13	C (7.1% mol)	-	100	3	78
14	C (7.1% mol)	-	80	3	-
15	C (1.9% mol)	-	130	3	24
16	C (13.4% mol)	-	130	3	84
17	C (16.1% mol)	-	130	3	86

* Isolated yield – A: Na_2SiO_3 (with 0.5% w/w of SnFe_2O_4); B: Na_2SiO_3 (with 1% w/w of SnFe_2O_4); C: Na_2SiO_3 (with 2% w/w of SnFe_2O_4)

Table 2: preparation of **1d-5d**, **1e-7e**, **1f-7f**, and **1g-3g** using Na_2SiO_3 (with 2% w/w of SnFe_2O_4) (7.1% mol).

Entry	Aldehyde	Product	Method A	Method B	Method C
			Time (h)/ Yield (%)*	Time (h)/ Yield (%)*	Time (h)/ Yield (%)*
1	Benzaldehyde	1d	3/91	2.5/85	2.5/93
2	4-Methylbenzaldehyde	2d	3/66	3/89	3/91
3	4-Methoxybenzaldehyde	3d	3/69	3/86	3/87
4	2,4-diChlorobenzaldehyde	4d	3/80	2.5/90	2.5/93
5	4-Chlorobenzaldehyde	5d	1.5/81	1.5/95	1.5/93
6	Benzaldehyde	1e	4/86	3.5/89	3/96
7	4-Methylbenzaldehyde	2e	5/81	4/94	3.5/91
8	4-Methoxybenzaldehyde	3e	5/85	4/88	3.5/90
9	2,4-diChlorobenzaldehyde	4e	4/79	3/96	2.5/95
10	4-Chlorobenzaldehyde	5e	2/87	1.5/93	1.5/90
11	4-Bromobenzaldehyde	6e	2/85	1.5/97	1.5/89
12	2-Chlorobenzaldehyde	7e	3/80	3/86	2.5/94
13	Benzaldehyde	1f	4/84	3/80	2.5/90
14	4-Methylbenzaldehyde	2f	5/73	4/79	3.5/88
15	4-Methoxybenzaldehyde	3f	5/72	4/86	3.5/82
16	2,4-diChlorobenzaldehyde	4f	5/71	4/88	3.5/89
17	4-Chlorobenzaldehyde	5f	2/80	2/89	1.5/90
18	4-Bromobenzaldehyde	6f	2/86	2/96	1.5/94
19	2-Chlorobenzaldehyde	7f	4/74	3.5/77	3/87
20	4-Chlorobenzaldehyde	1g	3/89	2.5/91	2/90
21	4-Bromobenzaldehyde	2g	3/84	2.5/96	2/93
22	4-Methoxybenzaldehyde	3g	4/78	3.5/90	3/88

* Isolated yields – Method A: solvent-free, 130°C; Method B: ultrasonic irradiation (US), 120°C; Method C: HSBM technique, 120°C

3 Conclusion

A mixture of Na_2SiO_3 with three different proportions of SnFe_2O_4 nano-particles was prepared, characterized by XRD, FE-SEM techniques and subsequently, was used for the preparation of **1d-5d**, **1e-7e**, **1f-7f**, and **1g-3g** in high yields. The high basic power of sodium silicate is decreased by adding SnFe_2O_4 nanoparticles which reduce the adverse reactions and disorientation, and increased the selectivity of the catalyst.

Experimental

The solvents, reactants and chemicals used in this study are from the Merck and Sigma-Aldrich Chemical Companies. The XRD patterns were taken in a PHILIPS PW3040 device. NMR spectra were recorded in a Bruker Avance DPX 400 MHz instrument in DMSO-d_6 as solvent relative to TMS (0.00 ppm). A Heraeus CHN-O-Rapid analyzer was used for elemental analysis. FE-SEM

photographs are taken using the FEI NOVA NANOSEM 450 photographic apparatus.

Preparation of SnFe_2O_4 nanoparticles

Two different solutions were prepared. The first solution was made up of SnCl_2 (1 mmol) and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (2 mmol) in 100 mL of ethanol. The second solution contains 20 mL ammonia in 40 mL of distilled water. The second solution is added slowly to the first solution under stirring. When the sedimentation process was completed, the solution is released for 30 min. The desired precipitate is then separated by a filter paper and washed with distilled water. Finally, the mixture was calcined at 500°C.

Preparation of SnFe_2O_4 /sodium silicate powder

SnFe_2O_4 nanoparticles are added to a solution of sodium silicate (1g Na_2SiO_3 in 10 mL H_2O) with a ratio of 0.5% w/w SnFe_2O_4 /sodium silicate and heated up to 100°C for

Scheme 2: proposed mechanism for the synthesis of 5-amino-7-aryl-2,4-dioxo-2,3,4,4a,7,7a,8,9,10,11-decahydro-1H-benzo[i]quinazoline-6-carbonitriles.

60 min, until a solid homogeneous mixture is obtained. Two additional samples were prepared with 1% and 2% w/w of SnFe₂O₄ by the same procedure.

Synthesis of 1H-benzo [i] quinazoline-6-carbonitrile derivatives

Method A:

A mixture of cyanoacetamide (3 mmol), cyclohexanone (1.2 mmol), benzaldehyde (1 mmol) and nanocatalysts (7.1% mol) are heated at 130°C until the reaction is complete (TLC monitoring). After completion of the reaction, the mixture is cooled to ambient temperature and mass was dissolved in hot ethanol and the insoluble catalyst is separated off by the filter paper. The resulting solution is concentrated until the evaporated solvent and sediments are recrystallized in cold watery ethanol and subsequently washed with diethyl ether to yield the pure product.

The reaction was also carried out with benzaldehyde derivatives.

Next, the reaction was carried out with all of the conditions described above with tetrahydro-4H-thiopyran-

4-one (1.2 mmol) and cyclopentanone (1.2 mmol) instead of cyclohexanone.

Method B:

The mixture was ultra-sonicated at 120°C. The procedure is similar with method A.

Method C:

The mixture was milled at 120°C. The procedure is similar with method A.

The mixture was milled in a stainless steel grinding vial (10 mL volume) equipped with a stainless steel ball (diameter: 6 mm; mass: 1.04 g) for appropriate times at 25 Hz and 120°C.

Conflict of interest: There is no conflict of interest to be reported.

Acknowledgements: We are thankful to the Najafabad Branch, Islamic Azad University research council for partial support of this research.

References

- Abaszadeh M., Roudbaraki S.J., Ghashang M., Effect of Liquid Glass Composition on the Catalytic Preparation of Pyrano[2, 3-d] pyrimidine Derivatives. *Org. Prep. Proced. Int.*, 2019, 51, 255-269.
- Daramola M.O., Nkazi D., Mtshali K., Synthesis and evaluation of catalytic activity of calcined sodium silicate for transesterification of waste cooking oil to biodiesel. *Int. J. Renew. Energy Res.*, 2015, 5, 517-523.
- Ebnesajjad S., Handbook of Adhesives and Surface Preparation Technology, Applications and Manufacturing Plastics Design Library, 2011, 137-183.
- El-Brollosy N.R., Synthesis of new quinazoline-2,4(1H,3H)-dione non-nucleoside analogues of the reverse transcriptase inhibitor TNK-651. *J. Chem. Res.*, 2007, 358-361.
- Fazlinia A., Sheikh S., Metal silicates: efficient catalysts for the three-component preparation of 2-amino-5-oxo-4-aryl-4,5-dihydroindeno[1,2-b]pyran-3-carbonitrile derivatives. *Main Group Met. Chem.*, 2018, 41, 47-52.
- Ghashang M., Mansoor S.S., Aswin K., Synthesis of 2, 3-dihydroquinazolin-4(1H)-ones catalyzed by succinimide-N-sulfonic acid as a mild and efficient catalyst. *Res. Chem. Intermediat.*, 2015, 41, 3447-3460.
- Ghashang M., Mansoor S.S., Aswin K., An efficient and environmentally friendly procedure for the synthesis of some novel 8-benzylidene-4-phenyl-3,4,5,6,7,8-hexahydro-1H-quinazolin-2-ones/thiones using tetrabutylammonium hexatungstate as a reusable heterogeneous catalyst under solvent-free conditions. *B. Kor. Chem. Soc.*, 2013, 34, 3289-3294.
- Ghashang M., Silica Supported Zinc (II) Chloride ($\text{SiO}_2\text{-ZnCl}_2$) as an Efficient Catalyst for the Eco-Friendly Synthesis of 2,3-Dihydroquinazolin-4(1H)-Ones. *Oriental J. Chem.*, 2012, 28, 1213-1218.
- Guo F., Peng Z., Dai J., Xiu Z., Calcined sodium silicate as solid base catalyst for biodiesel production. *Fuel Process. Technol.*, 2010, 91, 322-328.
- Guo F., Ning-Ning W.N., Xiu Z., Fang Z., Transesterification mechanism of soybean oil to biodiesel catalyzed by calcined sodium silicate. *Fuel*, 2012, 93, 468-472.
- Hei Y.-Y., Xin M., Zhang H., Xie X.-X., Mao S., Zhang S.-Q., Synthesis and antitumor activity evaluation of 4,6-disubstituted quinazoline derivatives as novel PI3K inhibitors. *Bioorg. Med. Chem. Lett.*, 2016, 26, 4408-4413.
- Lagaly G., Tufar W., Minihan A., Lovell A., »Silicates« in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, 2005.
- Li X.Q., The simple synthesis of quinazoline-2,4-dione derivatives using Boc strategy. *Chinese Chem. Lett.*, 2009, 20, 1201-1203.
- Long Y.D., Guo F., Fang Z., Tian X.F., Jiang L.Q., Zhang F., Production of biodiesel and lactic acid from rapeseed oil using sodium silicate as catalyst. *Bioresource Technol.*, 2011, 102, 6884-6886.
- Jiang B., Tu S.-J., Kaur P., Wever W., Li G., Four-Component Domino Reaction Leading to Multi-functionalized Quinazolines. *J. Am. Chem. Soc.*, 2009, 131, 11660-11661.
- Jiang B., Zhang T.-S., Fu R., Hao W.-J., Wang S.-L., Tu S.-J., A multi-component domino bicyclization strategy: direct access to skeletally diverse quinazoline collection. *Tetrahedron*, 2016, 72, 5652-5658.
- Ma J., Han B., Song J., Hu J., Lu W., Yang D., et al., Efficient synthesis of quinazoline-2,4(1H,3H)-diones from CO_2 and 2-aminobenzonitriles in water without any catalyst. *Green Chem.*, 2013, 15, 1485-1489.
- Maestri V., Tarozzi A., Simoni E., Cilia A., Poggesi E., Naldi M., et al., Quinazoline based α 1-adrenoreceptor antagonists with potent antiproliferative activity in human prostate cancer cell lines. *Eur. J. Med. Chem.*, 2017, 136, 259-269.
- Rasal K.B., Yadav G.D., Carbon Dioxide Mediated Novel Synthesis of Quinazoline-2,4(1H,3H)-dione in Water. *Org. Process Res. Dev.*, 2016, 20, 2067-2073.
- Sheikhan-Shamsabadi N., Ghashang M., Nano-basic silica as an efficient catalyst for the multi-component preparation of pyrano[2, 3-d]pyrimidine derivatives. *Main Group Met. Chem.*, 2017, 40, 19-25.
- Sheikh S., Fazlinia A., Preparation of Pyrido[2,3-b]indole Derivatives Using Silicates of Group 1 and 2 Metals. *J. Heterocyclic Chem.*, 2018, 55, 2291-2296.
- Yadav R.R., Guru S.K., Joshi P., Mahajan G., Mintoo M.J., Kumar V., et al., 6-Aryl substituted 4-(4-cyanomethyl) phenylamino quinazolines as a new class of isoform-selective PI3K-alpha inhibitors. *Eur. J. Med. Chem.*, 2016, 122, 731-743.
- Zhou J., Ji M., Yao H., Cao R., Zhao H., Wang X., et al., Discovery of quinazoline-2,4(1H,3H)-dione derivatives as novel PARP-1/2 inhibitors: design, synthesis and their antitumor activity. *Org. Biomol. Chem.*, 2018, 16, 3189-3202.