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Research Article

Synthesis of carbon-14-labelled pyronaridine tetraphosphate

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Abstract: Pyronaridine tetraphosphate is an antimalarial drug which is currently being widely investigated for use in the chemotherapy of malaria. We synthesized carbon-14-labelled pyronaridine tetraphosphate (^{14}C-PNDP, **5**) by a classical method and also by a microwave irradiation technique for use in biodistribution studies and pharmacokinetic analysis. The application of microwave irradiation facilitated the use of high temperatures resulting in decreased reaction time and employed far less amount of the starting material when compared with the classical method. ^{14}C-PNDP (**5**) thus synthesized had a chemical purity of >99% as determined by high-performance liquid chromatography (HPLC) and a radiochemical purity of >99% as determined by radio-HPLC. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: carbon-14; pyronaridine tetraphosphate; antimalarial drug; microwave irradiation

Introduction

Malaria is a vector-borne infectious disease that continues to be a major health problem in tropical regions of the world, particularly among children in sub-Saharan Africa.[1] Approximately 40% of the world's population live in areas with the risk of malaria. Each year about 300–500 million people suffer from acute malaria and 0.5–2.5 million die from the disease. Malaria is caused by four different species of the *Plasmodium* family of protozoa, *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Malarial parasites are spread by infecting successively two types of hosts: humans and female *Anopheles* mosquitoes. In humans, the parasites grow and multiply, first in liver cells and then in red blood cells. In the blood, successive broods of parasites grow inside red blood cells and destroy them, releasing daughter parasites ('merozoites') that continue the cycle by invading other red cells. The blood stage parasites are those that cause the symptoms of malaria. When certain forms of blood stage parasites ('gametocytes') are picked up by a female *Anopheles* mosquito during a blood meal, they start another different cycle of growth and multiplication in the mosquito. After 10–18 days, the parasites are found (as 'sporozoites') in the mosquito's salivary glands. When this *Anopheles* mosquito takes a blood meal on another human, the sporozoites are injected along with the mosquito's saliva and start another human infection where they parasitize liver cells. Thus, the mosquito carries the disease from one human to another, thus acting as a 'vector'.

Although malaria has been widely eradicated in many parts of the world, the global number of cases still continues to rise. The most important reason for this alarming situation is the rapid spread of malarial parasites which are resistant to antimalarial drugs, especially chloroquine, which is by far the most frequently used drug.[2] Thus, there is an urgent need to develop new antimalarial drugs and understand their mechanisms of action so that appropriate measures can be taken for their use in treating malaria.[3]

Pyronaridine tetraphosphate (PNDP, 2-methoxy-7-chloro-10 [3,5-bis (pyrrolidinyl-1-methyl-) 4-hydroxyphenyl] aminobenzyl-(b)-1,5-naphthyridine tetraphosphate, **3**) is a new highly active Mannich base antimalarial drug first developed in China (Scheme 1).[4] It is highly effective in treating malaria-infected patients in regions of chloroquine resistance.[5,6] PNDP (**3**) is a blood schizonticidal drug, active against the erythrocytic stages of the malarial parasite, and has already undergone extensive trials in humans against

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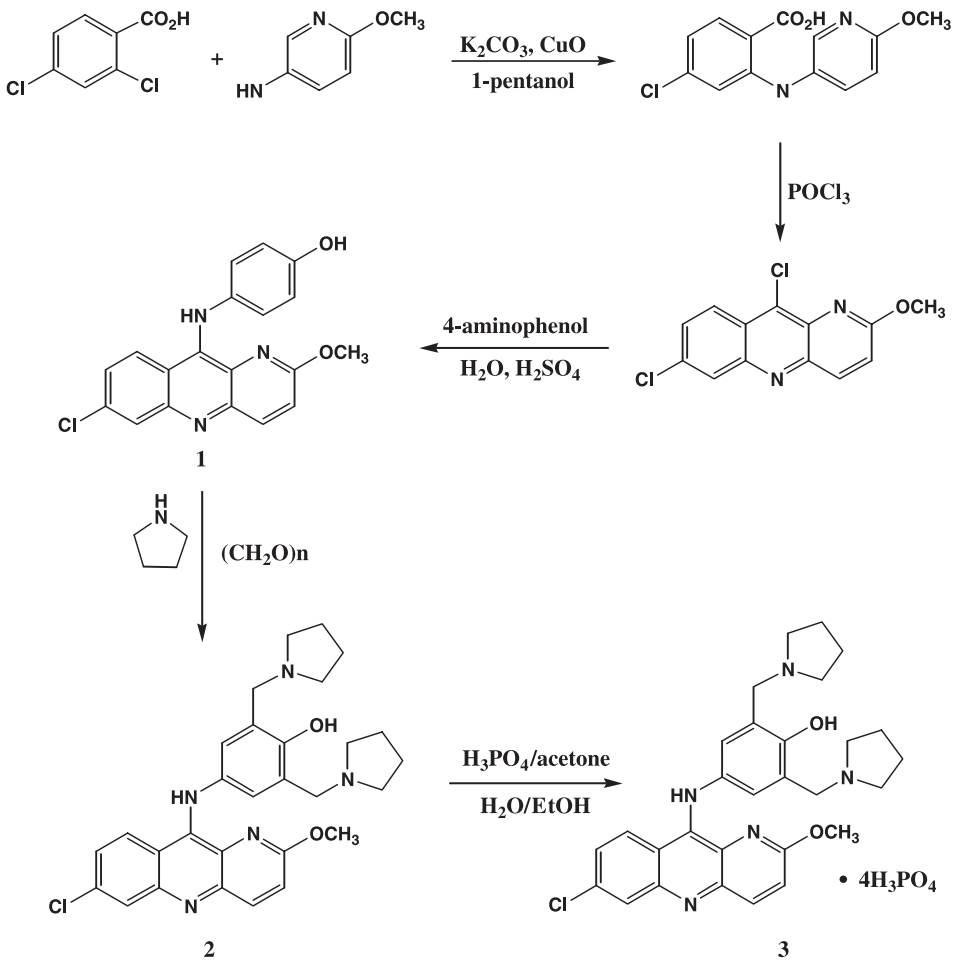

Scheme 1

both *P. falciparum* and *P. vivax*.[7] PNDP (**3**) was found to be highly effective against multidrug-resistant *P. falciparum* both in laboratory strains and clones.[8] It is also reported to be effective against rodent malaria parasite[9] and simian malaria.[10] Although several investigators have reported the pharmacological effect of PNDP (**3**), studies on its biodistribution and pharmacokinetics are not reported. In this paper we have detailed the method for the synthesis of PNDP (**3**) and ^{14}C-PNDP (**5**) for use in biodistribution and pharmacokinetic studies (Scheme 2). Since the classical method posed certain disadvantages, we decided to use microwave irradiation for the synthesis of PNDP (**3**) and ^{14}C-PNDP (**5**).

Results and discussion

Synthesis of PNDP (3) and ^{14}C-PNDP (5) by a classical method

Pyronaridine tetraphosphate (PNDP, **3**) was synthesized as described in Scheme 1.

PND (2-methoxy-7-chloro-10 [3,5-bis (pyrrolidinyl-1-methyl-) 4-hydroxyphenyl] aminobenzyl-(b)-1, 5-naphthyridine, **2**) was prepared by treating PNC (2-methoxy-7-chloro-10-(4′-hydroxyanilino)-[b]-1,5-naphthyridine, **1**) with a mixture of paraformaldehyde and pyrrolidine in anhydrous ethanol. The product was filtered to give PND (**2**) in 40% yield. PND (**2**) synthesized by the above reaction was reacted with ortho phosphoric acid. The product was filtered and washed with acetone, then dried under vacuum at 50°C to give the target compound **3** in 95% yield. The products provided satisfactory ^{1}H NMR, ^{13}C NMR, mass spectra (MS), infrared (IR) and elemental analysis data. The chemical purity of PNDP (**3**) determined by high-performance liquid chromatography (HPLC) was >99%. The retention time of PNDP obtained from a UV–vis detector was 18.9 min.

^{14}C-Pyronaridine tetraphosphate (^{14}C-PNDP, **5**) was also synthesized by the same manner as described above except using carbon-14-labelled paraformaldehyde instead of paraformaldehyde (Scheme 2). The

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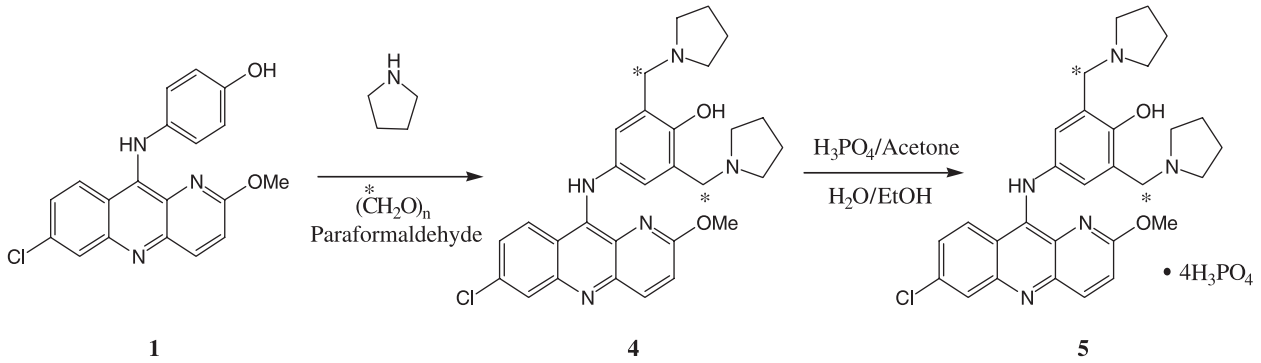

1 **4** **5**

Scheme 2

product provided satisfactory ^{1}H NMR data. The chemical purity and radiochemical purity of ^{14}C-PNDP were determined by HPLC. The retention times of both PNDP and ^{14}C-PNDP obtained from a UV–vis detector are similar at 18.9 and 19.1 min, respectively. Radiodetection of ^{14}C-PNDP revealed a single peak of >99% radiochemical purity ^{14}C-PNDP (**5**).

This classical method is not suitable for the radiolabelling of carbon-14 because of long reaction time (more than 12 h) and large amount of starting material (20 eq of paraformaldehyde) resulting in undesired radiation exposure, radiolysis and radioactive waste.

Synthesis of PNDP (3) ^{14}C-PNDP (5) by a microwave irradiation technique

Recently, microwave-assisted organic synthesis has moved to the forefront of chemical research and is set to revolutionize chemical synthesis.[11] Almost any type of organic reaction requiring heating or thermal conditions can be performed using microwave radiation. Microwave irradiation produces efficient internal heating (*in situ* heating), resulting in even heating throughout the sample, as compared with the wall heat transfer that occurs when an oil bath is applied as an energy source. Consequently, the tendency for the initiation of boiling is reduced, and superheating above the boiling point of the solvent is possible even at atmospheric pressure. Superheating can be generated rapidly in closed microwave-transparent vessels to temperatures as high as 100°C above the normal boiling point of a particular solvent.[12] It is this combination of rapid microwave heating and sealed vessel technology that is responsible for most of the observed rate enhancements seen in microwave-assisted organic synthesis. Microwave-assisted heating has been shown to be an invaluable optimization method since it reduces reaction times dramatically, typically from days or hours to minutes or seconds. Not only are microwaves able to reduce chemical reaction times drastically but are also known to reduce side reactions, increase yields and improve reproducibility.[13]

In the present investigation, we have detailed a novel procedure for the synthesis of PNDP (**3**) and ^{14}C-PNDP (**5**) using microwave irradiation. A mixture of paraformaldehyde and pyrrolidine (5–20 eq) in anhydrous ethanol (4 mL) was heated at 50–60°C for 1 h, then PNC (**1**) (1 eq) was added and the mixture was irradiated in a microwave reactor (Initatior 2.0, 400 W, Biotage, Sweden). The reaction was performed with various amounts of paraformaldehyde and various reaction temperatures as described in Table 1 (Scheme 3). The time required for the reaction to complete and product formation was noted. Purification of **2** and synthesis of **3** were performed essentially in the same manner described for the classical method. The optimum condition for the synthesis of **2** was determined based on the concentration of paraformaldehyde used, reaction time taken for the product formation and the reaction temperature at which maximum yield of the product was obtained (Table 1). In both classical and microwave irradiation methods, after purification procedures, the products provided satisfactory ^{1}H NMR, ^{13}C NMR, MS, IR data and element analysis.

On the basis of the optimum condition obtained from the above reactions, ^{14}C-labelled pyronaridine tetraphosphate (**5**) was synthesized by using ^{14}C-labelled formaldehyde by the microwave irradiation technique. A mixture of ^{14}C-labelled formaldehyde (1.4 g, 10 eq) and pyrrolidine (1.9 mL, 20 eq) in anhydrous ethanol (4 mL) was refluxed at 50–60°C for 1 h, then **1** (1 eq) was added and the mixture was irradiated for 25 min so as to reach a temperature of 140°C. The reaction gave 45% yield of **4**. **4** (1 eq) was mixed with distilled water (10 eq) and ortho phosphoric acid (7.7 eq) and stirred at room temperature for 30 min. The mixture was filtered and washed with distilled water. To the crude product **5** was added methanol (5.3 mL, 3 eq) and stirred at 5–10°C for

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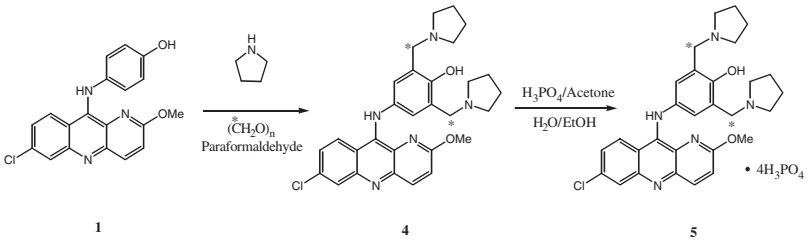
Table 1 Microwave irradiation conditions for the synthesis of pyronaridine (PND, **2**)



1 4 5

Run	Paraformaldehyde (eq)	Temperature (°C)	Reaction time (min)	Yield (%)
1	20	80	75	50
2	20	100	30	49
3	20	120	5	47
4	20	140	5	47
5	20	180	<2	46
6	10	80	165	46
7	10	100	55	47
8	10	120	45	48
9	10	140	25	49
10	10	180	<2	46
11	5	80	>360	46
12	5	100	>360	47
13	5	120	135	47
14	5	140	75	46
15	5	180	<2	44

1 h. The mixture was filtered and washed with acetone (16.3 mL, 20 eq). The solution of crude product **5** was mixed with 70% ethanol (4 mL, 14 eq) and ortho phosphoric acid (1.2 mL) and stirred at 60–65°C for 1 h. The mixture was allowed to cool to 10–20°C, filtered and washed with acetone, then dried under vacuum at 50°C to give 96% yield of **5**. The product provided satisfactory ^{1}H NMR data. The chemical purity and radiochemical purity of ^{14}C-PNDP were determined by HPLC. The retention times of both PNDP and ^{14}C-PNDP obtained from a UV–vis detector were similar at 18.9 and 19.1 min, respectively. Radio-detection of ^{14}C-PNDP revealed a single peak of >99% radiochemical purity ^{14}C-PNDP (**5**).

Microwave-assisted organic synthesis has been found to be suitable for the radio-labelling of carbon-14 because of shorter reaction time (25 min) and less amounts of starting material (10 eq of paraformaldehyde) than the ones of the classical method. This novel method results in a marked reduction of undesired radiation exposure, radiolysis and radioactive waste.

Stability test of ^{14}C-labelled pyronaridine tetraphosphate (^{14}C-PNDP, 5)

^{14}C-labelled pyronaridine tetraphosphate (**5**) was tested for its stability by analyzing the compound with radio-HPLC at appropriate time intervals, with **5** being stored at 4°C for up to 3 months. HPLC chromatograms taken before and after storage at 4°C for up to 3 months revealed a single peak of >99% radiochemical purity with the same retention time indicating **5** to be highly stable under standard storage conditions.

Experimental

General

2-Methoxy-7-chloro-10-(4′-hydroxyanilino)-[b]-1,5-naphthyridine (PNC, **1**) was obtained from Shinpoong Pharmaceutical, Co., Ltd., Seoul, Korea. All other chemicals were purchased from Sigma Chemical Co., USA and were used as such without any further purification.

Chemistry

The chemical purity of pyronaridine tetraphosphate (**3**) and the chemical purity and radiochemical purity of ^{14}C-labelled pyronaridine tetraphosphate (**5**) were determined by performing HPLC using an optimaPAK C_{18} (5 μm; 4.6 × 150 mm) column. HPLC solvents consisted of potassium phosphate buffer:acetonitrile (9:1) (solvent A) and potassium phosphate buffer:acetonitrile (2:8) (solvent B). One liter of the buffer (pH 2)

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consisted of KH_2PO_4 (1.36 g) and 1-octanesulfonic acid sodium salt hydrate (2.163 g). HPLC gradient: 0–17 min: a linear gradient to 70% A/30% B from 70% A/30% B; 17–25 min: a linear gradient to 60% A/40% B from 70% A/30% B; 25–30 min: a linear gradient to 60% A/40% B from 60% A/40% B; 30–31 min: a linear gradient to 70% A/30% B from 60% A/40% B. The flow rate was maintained at 1 mL/min and the column temperature was maintained at 40°C.

IR spectra were recorded on a Perkin-Elmer 1420 Ratio Recording Spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were recorded on an EA FISON, EA 1108, NMR Varian Inc., VNS 600 spectrophotometer. MS were obtained on a Matrix-assisted laser desoption ionization mass spectrophotometer system, Voyager TMDE-STR, Proteomics Analyser (Applied Biosystems Inc.). All chromatographic separations were monitored by TLC analyses and performed using glass plates precoated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Solvent removal was accomplished with aspirator pressure using a rotary evaporator.

Synthesis of pyronaridine tetraphosphate (PNDP, 3) by a classical method

Synthesis of pyronaridine (PND, 2) from 2-methoxy-7-chloro-10-(4′-hydroxyanilino)-[b]-1,5-naphthyridine (PNC, 1). A mixture of paraformaldehyde (2.8 g, 20 eq) and pyrrolidine (6.7 mL, 20 eq) in anhydrous ethanol (16.7 mL) was refluxed at 50–60°C for 1 h. **1** (1.67 g, 1 eq) was added and stirred at 45–55°C for 12–14 h. The mixture was washed with distilled water (16.7 mL). The residue was dissolved in methanol (16.7 mL) and stirred at 5–10°C for 2 h and filtered. The residue was washed with excessive methanol, then the residue was dissolved in dimethyl sulfoxide (DMSO) and dichloromethane (10.2 mL, $v : v = 1 : 1$) and stirred at 55–60°C for 3 h. The mixture was filtered and washed with methanol (5.1 mL), then dried to give 40% yield of **2**. IR (KBr): ν 3300, 2954, 2777, 1618, 1558, 1518, 1493, 1466, 1374, 1270, 1068, 1095, 1004, 1000, 927, 866, 834, 806 cm^{-1}; ^1H NMR (CD_3OD): δ 1.82 (t, 8 H, CH_2), 2.61 (s, 8 H, CH_2), 3.75 (s, 4 H, $ArCH_2$), 4.06 (s, 3 H, OCH_3), 7.01 (s, 2 H, ArH), 7.03 (s, 1 H, ArH), 7.28 (d, 1 H, ArH), 7.65 (d, 2 H, ArH), 7.88 (s, 2 H, ArH), 8.14 (d, 2 H, ArH); ^{13}C NMR (CD_3OD): δ 23.2, 53.3, 55.5, 114.6, 119.6, 113.0, 124.5, 124.8, 126.5, 127.2, 128.1, 133.5, 135.3, 138.9, 142.1, 146.1, 148.6, 154.8, 160.5; MS *m/z* 518.2 [M^+]; Anal. Calcd for $C_{29}H_{32}ClN_5O_2$: C 67.23, H 6.23, N 13.52. Found: C 67.18, H 5.96, N 12.85.

Synthesis of pyronaridine tetraphosphate (PNDP, 3) from pyronaridine (PND, 2). **2** (1 eq) synthesized by the above reaction was mixed with distilled water (10 eq) and ortho phosphoric acid (7.7 eq) and stirred at room temperature for 30 min. The mixture was filtered and washed with distilled water. To the crude product, methanol (5.3 mL, 3 eq) was added and stirred at 5–10°C for 1 h. The mixture was filtered and washed with acetone (16.3 mL, 20 eq). The solution of crude product was mixed with 70% ethanol (4 mL, 14 eq) and ortho phosphoric acid (1.2 mL) and stirred at 60–65°C for 1 h. The mixture was allowed to cool to 10–20°C, filtered and washed with acetone, then dried under vacuum at 50°C to give 95% yield of **3**. IR (KBr) ν 1551, 1491, 1387, 959 cm^{-1}; ^1H NMR (D_2O): δ 1.85 (s, 4 H, CH_2), 1.99 (s, 4 H, CH_2), 3.02 (s, 4 H, CH_2), 3.41 (s, 4 H, CH_2), 3.90 (s, 3 H, OCH_3), 4.31 (s, 4 H, $ArCH_2$), 7.10 (d, 1 H, ArH), 7.38 (t, 2 H, ArH), 7.44 (s, 2 H, ArH), 7.78 (s, 1 H, ArH), 8.06 (d, 1 H, ArH); ^{13}C NMR (D_2O): δ 21.4, 52.1, 52.9, 53.4, 110.7, 117.6, 121.0, 122.1, 123.7, 125.2, 126.4, 129.9, 130.3, 131.6, 138.8, 139.6, 151.3, 153.5, 159.9; MS *m/z* 518.2 [M^+-(H_3PO_4)]; Anal. Calcd for $C_{29}H_{32}ClN_5O_2$: C 38.27, H 4.87, N7.70. Found: C 38.03, H 5.26, N 7.53.

Synthesis of ^{14}C-labelled pyronaridine tetraphosphate (^{14}C-PNDP, 5) by a classical method

A mixture of ^{14}C-labelled paraformaldehyde (2.8 g, 20 eq) and pyrrolidine (6.7 mL, 20 eq) in anhydrous ethanol (16.7 mL) was refluxed at 50–60°C for 1 h. **1** (1.67 g, 1 eq) was added and stirred at 45–55°C for 12–14 h. The mixture was washed with distilled water (16.7 mL). The residue in methanol (16.7 mL) was stirred at 5–10°C for 2 h and filtered. The residue was washed with excessive methanol, then the residue was dissolved in DMSO and dichloromethane (10.2 mL, $v : v = 1 : 1$) and stirred at 55–60°C for 3 h. The mixture was filtered and washed with methanol (5.1 mL), then dried to give 36% yield of **5**: ^1H NMR (D_2O): δ 2.08 (s, 4 H, CH_2), 2.19 (s, 4 H, CH_2), 3.22 (s, 4 H, CH_2), 3.63 (s, 4 H, CH_2), 4.08 (s, 3 H, OCH_3), 4.49 (s, 4 H, $ArCH_2$), 7.24 (d, 1 H, ArH), 7.52 (t, 2 H, ArH), 7.59 (s, 2 H, ArH), 7.90 (s, 1 H, ArH), 8.20 (d, 1 H, ArH). **4** (1 eq) synthesized by the above reaction was mixed with distilled water (10 eq) and ortho phosphoric acid (7.7 eq) and stirred at room temperature for 30 min. The mixture was filtered and washed with distilled water. To the crude **5**, methanol (5.3 mL, 3 eq) was added and stirred at 5–10°C for 1 h. The mixture was filtered and washed with acetone (16.3 mL, 20 eq). The solution of crude **5** was mixed with 70% ethanol (4 mL, 14 eq) and ortho phosphoric acid (1.2 mL) and stirred at 60–65°C for 1 h. The mixture was allowed to cool to 10–20°C, filtered

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and washed with acetone, then dried under vacuum at 50°C to give 94% yield of **5**: ^{1}H NMR (D_2O): δ 1.85 (s, 4 H, CH_2), 1.99 (s, 4 H, CH_2), 3.02 (s, 4 H, CH_2), 3.41 (s, 4 H, CH_2), 3.90 (s, 3 H, OCH_3), 4.31 (s, 4 H, $ArCH_2$), 7.10 (d, 1 H, ArH), 7.38 (t, 2 H, ArH), 7.44 (s, 2 H, ArH), 7.78 (s, 1 H, ArH), 8.06 (d, 1 H, ArH).

Synthesis of pyronaridine tetraphosphate (PNDP, 3) by a microwave irradiation technique

A mixture of paraformaldehyde and pyrrolidine (1.9 mL, 20 eq) in anhydrous ethanol (4 mL) was refluxed at 50–60°C for 1 h, then **1** (0.4 g, 1 eq) was added and the mixture was irradiated in a microwave reactor (Initatior 2.0, 400 W, Biotage, Sweden). The reaction was performed under the conditions of various amounts of paraformaldehyde and various reaction temperatures as described in Table 1. The time required for the reaction to complete and product formation was noted. Purification of **2** and synthesis of **3** were performed essentially in the same manner described for the classical method. The optimum condition for the synthesis of **2** was determined based on the concentration of paraformaldehyde used, reaction time taken for the product formation and the reaction temperature at which maximum yield of the product was obtained (Table 1).

Synthesis of ^{14}C-labelled pyronaridine tetraphosphate (^{14}C-PNDP, 5) by a microwave irradiation technique

On the basis of optimum condition obtained from the above reactions, ^{14}C-labelled pyronaridine tetraphosphate (**5**) was synthesized by using ^{14}C-labelled formaldehyde by microwave irradiation technique. A mixture of ^{14}C-labelled paraformaldehyde (1.4 g, 10 eq) and pyrrolidine (1.9 mL, 20 eq) in anhydrous ethanol (4 mL) was refluxed at 50–60°C for 1 h, then **1** (1 eq) was added and the mixture was irradiated for 25 min so as to reach a temperature of 140°C. The product gave 45% yield of **5**. **4** (1 eq) was mixed with distilled water (10 eq) and ortho phosphoric acid (7.7 eq) and stirred at room temperature for 30 min. The mixture was filtered and washed with distilled water. To the crude **5**, methanol (5.3 mL, 3 eq) was added and stirred at 5–10°C for 1 h. The mixture was filtered and washed with acetone (16.3 mL, 20 eq). The solution of crude **5** was mixed with 70% ethanol (4 mL, 14 eq) and ortho phosphoric acid (1.2 mL) and stirred at 60–65°C for 1 h. The mixture was allowed to cool to 10–20°C, filtered and washed with acetone, then dried under vacuum at 50°C to give 96% yield of **5**.: ^{1}H NMR (D_2O): δ 2.08 (s, 4 H, CH_2), 2.19 (s, 4 H, CH_2), 3.22 (s, 4 H, CH_2), 3.63 (s, 4 H, CH_2), 4.08 (s, 3 H, OCH_3), 4.49 (s, 4 H, $ArCH_2$), 7.24 (d, 1 H, ArH), 7.52 (t, 2 H, ArH), 7.59 (s, 2 H, ArH), 7.90 (s, 1 H, ArH), 8.20 (d, 1 H, ArH).

The chemical purity of **3** and **5** was determined by HPLC (UV–vis detector) and the radiochemical purity of **5** was determined by HPLC (radiodetector). The HPLC chromatograms for both **3** and **5** obtained from a UV–vis detector revealed a single peak with similar retention time of 18.9 min (95% yield) and 19.1 min (94% yield), respectively, indicating a chemical purity of >99%. The HPLC chromatogram for **5** obtained from a radiodetector also revealed a single peak indicating >99% radiochemical purity. **2** and **3** also provided satisfactory ^{1}H NMR, ^{13}C NMR, MS, IR data and element analysis.

Stability test of ^{14}C-labelled pyronaridine tetraphosphate (^{14}C-PNDP, 5)

^{14}C-labelled pyronaridine tetraphosphate (**5**) was tested for its stability by analyzing the compound with radio-HPLC at appropriate time intervals, with **5** being stored at 4°C for up to 3 months.

Conclusions

A novel method for the synthesis of PNDP (**3**) and ^{14}C-PNDP (**5**) was developed using microwave irradiation technique. This method considerably reduced the overall reaction time and also increased the yield compared with the classical method. The compounds also provided satisfactory instrumental analysis data. Further, ^{14}C-PNDP (**5**) was found to be stable for up to 3 months when stored at 4°C. This isotopically labelled derivative was used for *in vitro* pre-clinical studies. The result of one of these studies of ^{14}C-PNDP (**5**) synthesized by the microwave irradiation technique described here will be reported in a timely manner.

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