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Synthesis of a series of carbon-14 labelled 4-aminoquinazolines and quinazolin-4 (3H)-ones

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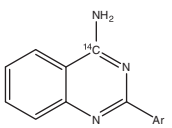
4-Aminoquinazolines and quinazolin-4 (3H)-ones, both labelled with carbon-14 in the 4-position, were prepared from 2-aminobenzonitrile-[cyano-^{14}C] and 2-aminobenzoic acid-[carboxy -^{14}C] or 2-amino- benzamide-[carboxy -^{14}C], respectively, using rapid, one-pot procedures under microwave enhanced conditions.

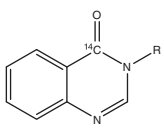
Keywords: quinazolines; quinazolin-4-ones; microwave heating; 2-aminobenzamide; carbon-14

Introduction

Quinazolines have been a rich source of biologically active molecular entities and are related to a wide family of compounds with well-known pharmacological properties.[1–3] Among the different substitution patterns that are known, 4-aminoquinazolines and quinazolin-4 (3H)-ones are important because of their potential biological and pharmaceutical activities. 4-Aminoquinazolines are useful as fungicides and anti-inflammatory, anti-cancer, anti-microbial and anti-hypertensive agents.[4,5] Quinazolin-4 (3H)-ones have also emerged as an important class of nitrogen containing heterocyclic compounds because of their pharmacological and therapeutic properties and show anti-bacterial, anti-fungal, anti-malarial, anti-hypertensive, activity. These compounds also show effects on the central nervous system (CNS) and have sedative-hypotic and anti-convulsant, anti-parkinsonism, anti-histaminic properties.[6–8] To further elucidate the mechanism of action and investigate the pharmacokinetics and drug metabolism of these compounds, the preparation of suitable metabolically stable carbon-14 labels were required.[9] This paper reports the Synthesis of Carbon-14 labelled 4-aminoquinazolines (**1a, b, c**) and quinazolin-4 (3H)-ones (**2a, b, c**).



1a:(Ar: 2-thiophenyl)
b:(Ar: m-cyanophenyl)
c:(Ar: phenyl)



2a: (R= phenyl)
b: (R: 4-chlorophenyl)
c: (R: benzyl)

Discussion

Our approach to the synthesis of 4-aminoquinazolines-[4-^{14}C] 1a, b, c is shown in Scheme 1. 2-Aminobenzonitrile-[cyano-^{14}C] **5** was derived from the reaction of 2-iodoaniline **4** with potassium[^{14}C] cyanide **2** and cuprous iodide **3** in hot DMF, in good yield.[10,11] **5** could then be converted to 4-aminoquinazoline-[4-^{14}C] **1**, by treatment with arylnitrile **6** in the presence of t-BuOK under microwave irradiation, in the absence of solvent. Product **1** was obtained in good yield.[12]

Our approach to the synthesis of quinazolin-4(3H)-ones-[4-^{14}C] **2a, b, c** is shown in Scheme 2. **5** is converted to 2-aminobenzoic acid-[carboxy-^{14}C] **6a** by treatment with aqueous base.[13] A mixture of **6a** and amine 7 and formic acid **8** was then irradiated under microwave condition in the absence of solvent or any dehydrating agents. In order to control the reaction the irradiation was carried out in two stages with a cooling time between them. In both cases however, to ensure optimum yield of products, an excess of formic acid **8** had to be employed.[14–16] On the other hand, using the known Niementowski reaction, [17,18] the condensation of formamide **9** with **6a** under microwave irradiation, gave the desired product **2** in a few minutes.

The conversion of 2-aminobenzonitrile-[cyano-^{14}C] **5** to 2-aminobenzoic acid-[carboxy-^{14}C] **6a** by treatment with aqueous base is a long procedure and the work up and collection of 2-aminobenzoic acid-[carboxy-^{14}C] **6a** from aqueous media is very difficult. An improved process using 2-aminobenzamide-[carboxy-^{14}C] **6b** instead of **6a** was therefore developed. In this route, **5** was converted to **6b** using basic hydrogen peroxide in DMSO in good yield (90%, 1 h).[19] A mixture of **6b** and formamide **9**, in the presence of N,N-dimethylacetamide, introduced as a fusion accelerator was irradiated under microwave condition to give quinazolin-4 (3H)-ones (**2a, b, c**) in good yield.

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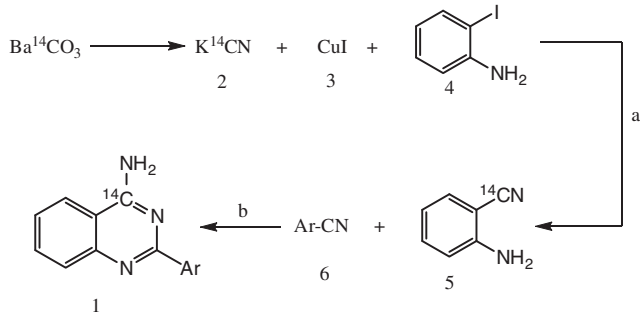
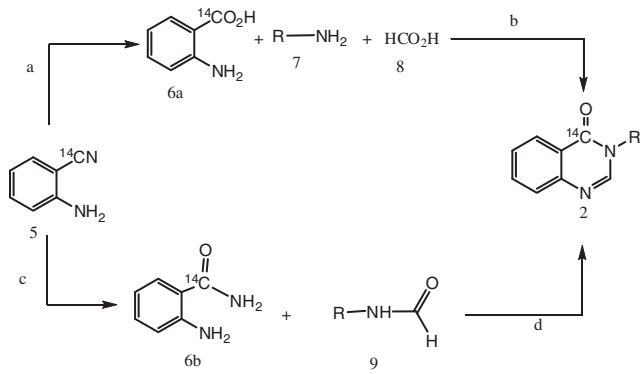


Scheme 1. (a) DMF and (b) KO-t-Bu, MW.



Scheme 2. (a) KOH/EtOH; (b) MW; (c) K_2CO_3, DMSO, H_2O_2 30%; (d) MW, N,N-dimethylacetamide.

Experimental

Barium [^{14}C]carbonate was converted to potassium [^{14}C]cyanide according to the standard procedure.[20] IR spectra were recorded on a Bruker FT-IR, Vector 22 instrument and the ^{1}H- NMR spectra were recorded on a Varian unity plus 400 spectrometer (400 MHz). HPLC: equipment consisted of: a waters 1525 Binary HPLC pump, a waters 2487 Dual λ absorbance detector, a waters Breeze Data processing system, Column: μ Bondapak$_{18}$ (150 × 4.6 mm) and 5 μm diameters and uv detection at λ = 254 nm. The isocratic elution was used for chromatographic separation at room temperature. The eluent was CH_3CN: H_2O (60:40) with flow rate: 1 mL/min. Microwave irradiation was carried out in a national oven, model 5250 at 2450 MHz. All the experiments were performed in an efficient ventilated enclosure, in order to avoid exposure with vapors. Radioactivity was determined using a Beckman LS6500 liquid scintillation spectrometer. Mass spectra were obtained on a Finnigan TSQ-70 instrument.

2-Amino-benzonitrile-[cyano-^{14}C] 5

Cuprous iodide **3** (815 mg) was ground finely and dried in the reaction flask under high vacuum by heating with a hot air gun and cooled under nitrogen. Potassium [^{14}C]cyanide (318 MBq, 228 mg) **2** was added slurried in dry DMF (10 ml), followed by 2-iodoaniline **4** (1718 mg). The mixture was heated at reflux, under nitrogen, for 10 h. On cooling a solution of potassium cyanide (1.2 g) in water (50 ml) and ethyl acetate (20 ml) were added and the mixture stirred vigorously for 15 min. The layers were separated, the aqueous thoroughly extracted with ethyl acetate, the combined organics washed three times with water, dried over anhydrous $MgSO_4$, filtered and the solvent carefully evaporated. The crude product was purified by silica gel chromatography using ethyl acetate:hexane (1:4) as eluant to give 2-aminobenzonitrile [cyano-^{14}C] (272 MBq, 354 mg) **5** (radiochemical yield: 85.5 %). (R_t: 2.3 min), ^{1}H-NMR ($CDCl_3$, TMS): δ7.4, d, 1H; δ7.34, t, 1H; δ6.74–6.78, m, 2H; δ4.47,s, 2H, MS (70 eV): *m/z* = 120 (M^+).

4-Amino-2-(2-thiophenyl)-quinazoline-[4-^{14}C] 1a

A mixture of 2-aminobenzonitrile-[cyano-^{14}C] (76.84 MBq, 100 mg) **5**, 2-thiophenenitrile (92 mg) **6a** and potassium *tert*-butoxide (10 mg) in a test tube was heated in a domestic microwave oven until no starting materials were observed by TLC(700 W, 1.5 min.). The crude reaction was purified by crystallization from methanol to afford **1a** (63.77 MBq, 160 mg, 83%). (R_t: 3.15 min),^{1}H-NMR (CD_3OD, TMS): δ8.19, d, 1H; δ8.14,d, 1H; δ7.89, m, 2H; δ7.68, d, 1H; δ7.55, m, 1 H; δ7.28, t, 1H., MS (70 eV): *m/z* = 229 (M^+).

4-Amino-2-(3-cyanophenyl)-quinazoline-[4-^{14}C] 1b

1b was prepared according to the above-described procedure by heating **5** (76.84 MBq, 100 mg) and 1,3-dicyanobenzene (108 mg) **6b** under microwave irradiation (700 W, 2 min, radiochemical yield: 80%). (R_t: 3.5 min),^{1}H-NMR (Cl_3CD, TMS): δ8.84, s, 1H; δ8.78,d, 1H; δ7.95, d, 1H; δ7.72–7.82, m, 3H; δ7.52–7.61, m, 2H; δ5.81, brs, 2H., MS (70 eV): *m/z* = 248 (M^+).

4-Amino-2-phenyl-quinazoline-[4-^{14}C] 1c

1c was prepared according to the above-described procedure by heating **5** (76.84 MBq, 100 mg) and benzonitrile (87 mg) **6c** under microwave irradiation(700 W, 2 min, radiochemical yield: 87%).(R_t: 3.05 min),^{1}H-NMR (Cl_3CD, TMS): δ8.50, d, 2H; δ7.98,m, 1H; δ7.72–7.82, m, 2H; δ7.42–7.57, m, 4H; δ5.73, brs, 2H., MS (70 eV): *m/z* = 223 (M^+).

2-Aminobenzoic acid-[carboxyl-^{14} C] 6a

A mixture of 2-amino-benzonitrile-[cyano-^{14}C] **5** (1500 mg, 1152.5 MBq) and potassium hydroxide (34.6 g) in Water(577 ml) was stirred and heated under reflux for 5 h affording a clear brown solution. After cooling to room temperature, the reaction mixture was neutralized with HCl(conc.) to pH = 3–4, when precipitation occurred. The reaction mixture was extracted with ethyl acetate (5 × 300 ml). The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo affording **6a** (1500 mg, 991.2 MBq) in 86% yield(R_t: 1.35 min), MS (70 eV): *m/z* = 139 (M^+).

3-Phenyl-quinazolin-4-one-[4-^{14}C] 2a

A mixture of 2-aminobenzoic acid-[carboxyl-^{14}C] **6a** (1370 mg, 905.29 MBq), formic acid **8** (690 mg) and aniline **7a** (1210 mg) contained in a tall beaker was placed in the microwave oven and the beaker was covered with a stemless funnel and irradiated for 3 min at power 210 W. After about 5 min, as it cooled to room temperature, the reaction mixture was irradiated again for 4 min at 385 W. Then the reaction mixture was dissolved in hot ethanol–water from which the product crystallized. The product was recrystallized from 1M NaOH-ethanol (2:5) to give (1600 mg, 651.81 MBq) of **2a** (radiochemical

yield: 72%). (R_t: 2.5 min),^{1}H-NMR (Cl_3CD, TMS): δ8.36, dd, 1H; δ8.14, s, 1H; δ7.55–7.58, m, 2H; δ7.26–7.45, m, 6H., MS (70 eV): $m/z = 224$ (M^+).

3-(4-Chloro-phenyl)-quinazolin-4-one-[4-^{14}C] 2b

2b was prepared according to the above-described procedure by heating a mixture of 2-aminobenzoic acid-[carboxyl-^{14}C] **6a** (1370 mg,905.29 MBq), formic acid **8** (690 mg) and 4-chloro-aniline **7b** (1275 mg) under microwave irradiation (3 min at 210 W and 3 min at 385 W radiochemical yield: 68%).(R_t: 3.2 min), ^{1}H-NMR (Cl_3CD, TMS): δ8.38, dd, 1H; δ8.10, s, 1H; δ7.79–7.83, m, 2H; δ7.35–7.59, m, 3H; δ7.38–7.40, m, 2H., MS (70 eV): $m/z = 258$ (M^+).

3-benzyl-quinazolin-4-one-[4-^{14}C] 2c

2c was prepared according to the above-described procedure by heating a mixture of 2-aminobenzoic acid-[carboxyl-^{14}C] **6a** (1370 mg,905.29 MBq), formic acid **8** (690 mg) and benzylamine **7c** (1390 mg) under microwave irradiation (3 min at 210 W, 2 and 6 min at 385 W radiochemical yield: 65%). (R_t: 2.8 min),^{1}H-NMR (Cl_3CD, TMS): δ8.34, dd, 1H; δ8.12, s, 1H; δ7.70–7.78, m, 2H; δ7.52–7.61, m, 1; δ7.33–7.37, m, 5H; δ5.21, s, 2H, MS (70 eV): $m/z = 238$ (M^+).

Alternative procedures for preparation of (2a–c)-[4-^{14}C]

Method I

3-Phenyl-quinazolin-4-one-[4-14C] 2a: A mixture of N-phenylformamide **9a** (1.21 g, 10 mmol), 2-aminobenzoic acid-[carboxyl-^{14}C] **6a** (1370 mg,905.29 MBq), and a few drops of N,N-dimethylacetamide were heated under microwave irradiation (6 min at 385 W). The resultant residue after crystallization from hot ethanol–water gave of **2a** (1776 mg, 724.23 MBq) (radiochemical yield: 80%). (R_t: 2.5 min), ^{1}H-NMR (Cl_3CD, TMS): δ8.36, dd, 1H; δ8.14, s, 1H; δ7.55–7.58, m, 2H; δ7.26–7.45, m, 6H., MS (70 eV): $m/z = 224$ (M^+).

3-(4-Chloro-phenyl)-quinazolin-4-one-[4-^{14}C] 2b: **2b** was prepared according to the above-described procedure by heating a mixture of 4-N-(4-chlorophenyl)formamide **9b** (1555 mg, 10 mmol), 2-aminobenzoic acid-[carboxyl-^{14}C] **6a** (1370 mg,905.29 MBq), and a few drops of N,N-dimethyl-acetamide under microwave irradiation (6 min at 385 W, radiochemical yield: 76%). (R_t: 3.2 min),^{1}H-NMR (Cl_3CD, TMS): δ8.38, dd, 1H; δ8.10, s, 1H; δ7.79−7.83, m, 2H; δ7.35–7.59, m, 3H; δ7.38–7.40, m, 2H., MS (70 eV): $m/z = 258$ (M^+).

3-benzyl-quinazolin-4-one-[4-^{14}C] 2c: **2c** was prepared according to the above-described procedure by heating a mixture of benzyl formamide **9c** (1350 mg, 10 mmol), 2-aminobenzoic acid-[carboxyl-^{14}C] **6a** (1370 mg,905.29 MBq), and a few drops of N,N-dimethylacetamide under microwave irradiation (6 min at 385 W, radiochemical yield: 71%). (R_t: 2.8 min),^{1}H-NMR (Cl_3CD, TMS): δ8.34, dd, 1H; δ8.12, s, 1H; δ7.70–7.78, m, 2H; δ7.52–7.61, m, 1; δ7.33–7.37, m, 5H; δ5.21, s, 2H., MS (70 eV): $m/z = 238$ (M^+).

2-Amino-benzamide[carboxyl-^{14} C] 6b: To a stirred solution of 2-aminobenzonitrile-[cyano-^{14}C] **5** (1111.78 MBq, 1447 mg) in DMSO (5.25 ml) cooled in an ice bath was added H_2O_2 (30%, 2.1 ml) and potassium carbonate (350 mg). The mixture was then allowed to warm up to room temperature. After one hour, distilled water (90 ml) and ethyl acetate (100 ml) were added to the mixture and the organic phase was separated, dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The product was purified by silica gel chromatography using chloroform:methanol (9:1) as eluant to give **6b** (998.64 MBq, 1500 mg). (R_t: 1.6 min), MS (70 eV): $m/z = 138$ (M^+).

Alternative procedures for preparation of (2a–c)-[4-^{14}C]

Method II

3-Phenyl-quinazolin-4-one-[4-^{14}C] 2a: A mixture of formanilide **9a** (1.21 g, 10 mmol), 2-amino-benzamide-[carboxy-^{14}C] **6b** (1360 mg, 905.43 MBq), and a few drops of N,N-dimethylacetamide were heated under microwave irradiation(6 min at 385 W). The resultant residue after crystallization from hot ethanol–water gave 1842 mg, 751.50 MBq of **2a** (radiochemical yield: 83%). (R_t: 2.5 min),^{1}H-NMR (Cl_3CD, TMS): δ8.36, dd, 1H; δ8.14, s, 1H; δ7.55–7.58, m, 2H; δ7.26–7.45, m, 6H., MS (70 eV): $m/z = 224$ (M^+).

3-(4-Chloro-phenyl)-quinazolin-4-one-[4-^{14}C] 2b: **2b** was prepared according to the above-described procedure by heating a mixture of 4-chloroformanilide **9b** (1555 mg, 10 mmol), 2-amino-benzamide-[carboxy-^{14}C] **6b** (1360 mg,905.43 MBq), and a few drops of N,N-dimethylacetamide under microwave irradiation(6 min at 385 W, radiochemical yield: 79%). (R_t: 3.2 min), ^{1}H-NMR (Cl_3CD, TMS): δ8.38, dd, 1H; δ8.10, s, 1H; δ7.79–7.83, m, 2H; δ7.35–7.59, m, 3H; δ7.38–7.40, m, 2H., MS (70 eV): $m/z = 258$ (M^+).

3-benzyl-quinazolin-4-one-[4-^{14}C] 2c: **2c** was prepared according to the above-described procedure by heating a mixture of benzyl formamide **9c** (1350 mg, 10 mmol), 2-amino-benzamide-[carboxy-^{14}C] **6b** (1360 mg,905.43 MBq), and a few drops of N,N-dimethylacetamide under microwave irradiation(6 min at 385 W, radiochemical yield: 74%). (R_t: 2.8 min),^{1}H-NMR (Cl_3CD, TMS): δ8.34, dd, 1H; δ8.12, s, 1H; δ7.70–7.78, m, 2H; δ7.52–7.61, m, 1; δ7.33–7.37, m, 5H; δ5.21, s, 2H., MS (70 eV): $m/z = 238$ (M^+).

Conclusion

In this paper, we have presented a convenient synthetic pathway for labelling of a series of 4-amino- quinazolines and quinazolin-4 (3H)-ones with carbon-14 by using rapid, one-pot procedures under microwave enhanced conditions.

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