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Bioorg Med Chem Lett. Author manuscript; available in PMC 2009 June 1.

Published in final edited form as:
Bioorg Med Chem Lett. 2008 June 1; 18(11): 3364–3368.

Synthesis and Anti-Breast Cancer Activities of Substituted Quinolines†

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Abstract

Promising anti-breast cancer agents derived from substituted quinolines were discovered. The quinolines were readily synthesized in large scale from a sequence of reactions starting from 4-acetamidoanisole. The Michael addition product was isolated as the reaction intermediate in the ring closing reaction of 4-amino-5-nitro-2-(3-trifluoromethylphenyloxy)anisole with methyl vinyl ketone leading to 6-methoxy-4-methyl-8-nitro-5-(3-trifluoromethylphenyloxy)quinoline (**14**). The amino function of 8-amino-6-methoxy-4-methyl-5-(3-trifluoromethylphenyloxy)quinoline, prepared from **14**, was connected to various side chains via alkylation with *N*-(3-iodopropyl)phthalimide, Michael addition with acrylonitrile, and reductive amination with various heterocycle carboxaldehydes, such as imidazole-4-carboxaldehyde, thiophene-2-carboxaldehyde, and 2-furaldehyde. Effects of the substituted quinolines on cell viability of T47D breast cancer cells using trypan blue exclusion assay were examined. The results showed that the IC_{50} value of 6-methoxy-8-[(2-furanylmethyl)amino]-4-methyl-5-(3-trifluoromethylphenyloxy)quinoline is 16 ± 3 nM, the lowest IC_{50} out of all the quinolines tested. IC_{50} values of three other quinolines are in the nanomolar range, a desirable range for pharmacological testing.

Keywords

synthesis of substituted quinolines; anti-breast-cancer agents; T47D breast cancer cells

Quinolines are known for their anti-malarial,[1–3] leishmanicidal,[4] antibacterial[5] and anticancer activities.[6–9] Recently, quinolines were examined in ATP-binding cassette drug transporter inhibition,[6] targeting tumor hypoxia,[7] modulation of multidrug resistance,[8] and tyrosine kinase inhibition.[9] Based on these literature results, we investigated substituted quinolines in search of novel anti-breast cancer compounds. After our initial anticancer screening, we focused on substituted quinolines with a skeletal structure derived from 8-amino-5-(aryloxy)-6-methoxy-4-methylquinoline,[1] by derivatizing its C8-amino side chain. We report

†This manuscript is dedicated to Professor E. J. Corey on the occasion of his 80th birthday.

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herein syntheses of new quinolines possessing amine, nitrile, imidate, amidine and heterocyclic functionalities in the C8-amino side chain, and their potent anti-breast cancer activities against T47D breast cancer cells. The synthetic substituted quinolines are summarzied in Figure 1.

We utilized a similar synthetic method leading to 5-(aryloxy)-4-methylprimaquine[1,10] by starting with 4-acetamidoanisole (**8**) via sequential C2 and C5 functionalizations followed by a ring closing reaction. Hence, 2-bromo-4-acetamino-5-nitroanisole (**10**)[10] was prepared from the bromination of compound **8** at C2 followed by nitration at C5. Displacement of bromide **6** with potassium 3-trifluoromethylphenoxide (**11**) in *N*,*N*-dimethylformamide (DMF) at 120° C gave 4-acetamino-5-nitro-2-(3-trifluoromethylphenyloxy)anisole (**12**). Removal of the acetyl protecting group of **12** with hydrochloric acid in ethanol afforded 4-amino-5-nitro-2-(3-trifluoromethylphenyloxy)anisole (**13**).

Various reaction conditions were studied to maximize the yield of the construction of the quinoline ring from compound **13** with methyl vinyl ketone.[2] Treatment of **13** with vinyl methyl ketone, arsenic acid and 85% phosphoric acid at 100 °C after 20 minutes,[8] a mixture of desired quinoline **14** and 1,4-adduct **15** along with starting material **13** was obtained in a ratio of 1:2:1. When the reaction was carried out at 120 °C for 20 minutes, a 7:1:1 ratio of compounds **14**:**15**:**13** was achieved (Scheme 2). The crude products were separated by silica gel column chromatography to give a 52% yield of compound **14**, 7% yield of compound **15**, and 7% recovery of **13**. A longer reaction time resulted in decomposition of the products and yields were not improved. The use of excess of vinyl methyl ketone did not improve the yield either. The 1,4-adduct, **15**, can be treated with arsenic acid and phosphoric acid under similar reaction conditions as that mentioned above to give quinoline **14** and amine **13** along with starting material **15** in a ratio of ~7:1:1. Hence, uses of a large excess of arsenic acid and 85% phosphoric acid may minimize the formation of intermediate **15**. The results suggest that adduct **15** is the reaction intermediate leading to quinoline **14**, but it also underwent reversed Michael addition reaction to provide amine **13** and vinyl methyl ketone. Since conjugated alkynones had been used in the construction of quinolines from aromatic amines,[4,11] amine **13** was treated with 3-butyn-2-one and arsenic acid and phosphoric acid at 100°C. Desired product **14** was isolated in a 24% yield along with 28% of recovery of starting material **13**. The 1,4-adduct was not detected, and various unidentifiable oligomers were obtained. The lower yield may contribute to the ease of polymerization of the terminal alkynone or the decomposition of the intermediate 1,4-adduct.

Quinoline **14** was converted to compound **16**, which serves as the precursor to produce various substituted quinolines depicted in Figure 1. Hence, reduction of the nitro function of **14** with iron powder in acetic acid-water under reflux gave a 96% yield of amino quinoline **16** (Scheme 3). Alkylation of **16** with iodide **17**[12] and sodium bicarbonate in DMF produced compound **18** which upon treatment with hydrazine in refluxing ethanol afforded quinoline **1**.

Quinolines **2** – **4** were synthesized through a Michael addition reaction of arylamine **16** with acrylonitrile in phenol[13] at 100°C in a sealed tube and gave adduct **2** (61% yield). No reaction was found when **16** was treated with acrylonitrile in refluxing ethanol.[14] Ethanolysis of quinoline **2** with HCl (gas) in ethanol[15] produced ethyl imidate **3**, which upon treatment with NH_3 (gas) in ethanol[16] at 50°C for 6 h afforded amidine **4** (57% yield) along with 13% of recovered starting material **3**.

Quinolines **5** – **7** were synthesized via a reductive amination of amine **16** and aldehydes (Scheme 4). Treatment of amine **16** with aldehyde **19** in methanol-acetic acid followed by sodium cyanoborohydride[17] furnished quinoline **5**. Similar treatment of amine **16** with aldehydes **20** and **21** separately afforded quinolines **6** and **7**, respectively. Aldehyde **19** was

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prepared from the oxidation of 4-hydroxymethylimidazole with manganese dioxide in methanol (99% yield).[18]

The effects of quinolines **1** – **7** on cell viability of T47D breast cancer cells using trypan blue exclusion assay were examined. The trypan blue exclusion assay provides a rapid and effective means in screening multiple drugs.[19] Assays for each compound were conducted in triplicate and the statistical significances are shown along with the IC_{50} values in Table 1. The results showed that the IC_{50} value of quinoline **7** is 16 ± 3 nM, the lowest IC_{50} out of all the quinolines tested. The weak inhibition of quinoline **6** may due to the oxidation of sulfur of the thiophene moiety during the two-day incubation with the T47D breast cancer cells. IC_{50} values of **1**, **2**, and **4** are in the nanomolar range, a desirable range for pharmacological testing. Compounds **16** and **18** did not inhibit T47D cell viability even at 10 μM concentration.

In conclusion, various substituted quinolines were synthesized from a tandem Michael addition followed by electrophilic aromatic substitution reaction of substituted aniline with vinyl methyl ketone, reduction of the nitro function, and alkylation of the resulting amine moiety. The synthetic sequence is short and amenable to large scale synthesis. Several of these compounds possess potent anticancer activities against T47D breast cancer cells in nM ranges. In particular, quinoline **7** showed an IC_{50} value of 16 ± 3 nM, and is worthy of further pharmacological studies. The absence of asymmetric center in these molecules alleviates the chiral synthesis and purification of enantiomers for bioevaluation. Variation of substituents of these lead compounds along with the mechanism of action of their anticancer activity is being studied and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We gratefully acknowledge financial support by EYRO113421 to D.J.T., NIH R01AG025500, NSF CHE-0555341 and American Heart Association 0750115Z to D.H.H., and NIH P20RR017686 to T.A.N.

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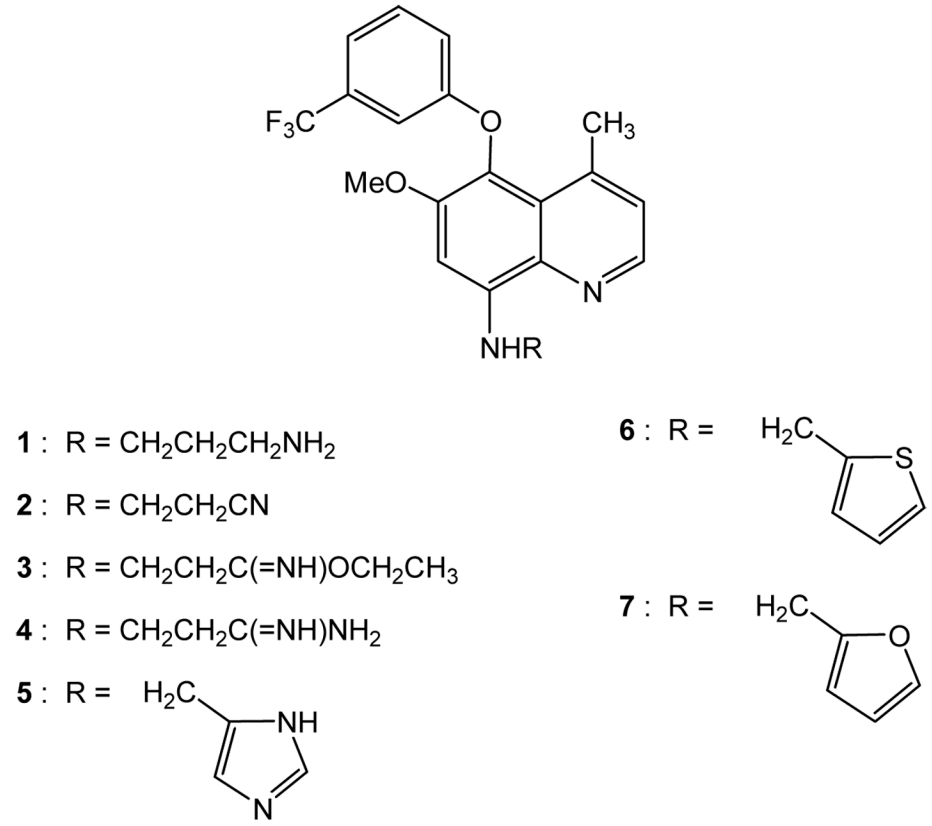

Figure 1.
Structural formulas of substituted quinolines

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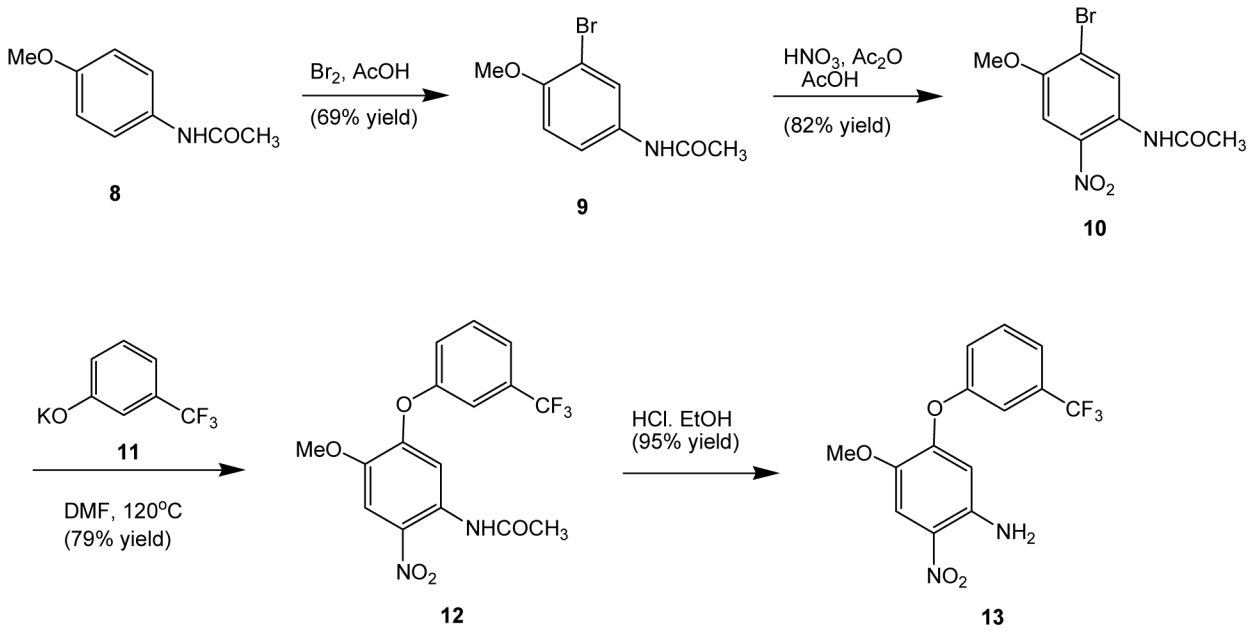

Scheme 1.
Preparation of 4-amino-5-nitro-2-(3-trifluoromethylphenyloxy)anisole (**13**)

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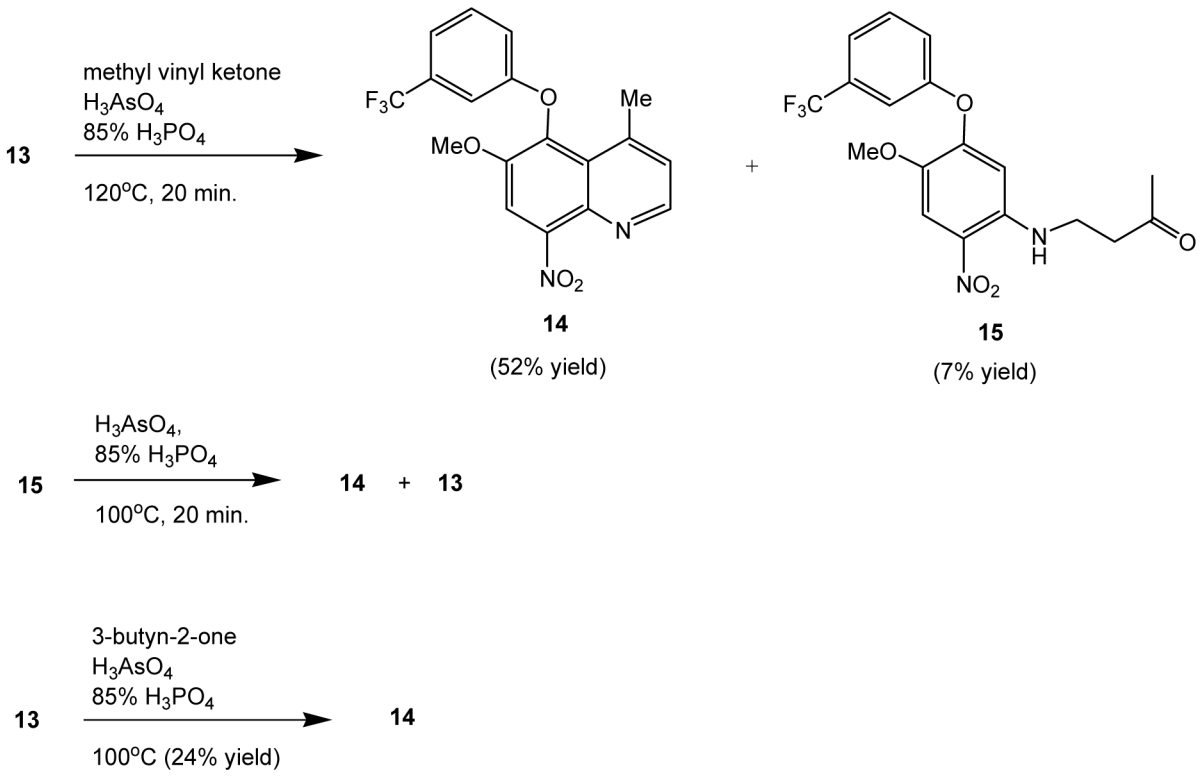

Scheme 2.
Preparation of quinoline 14.

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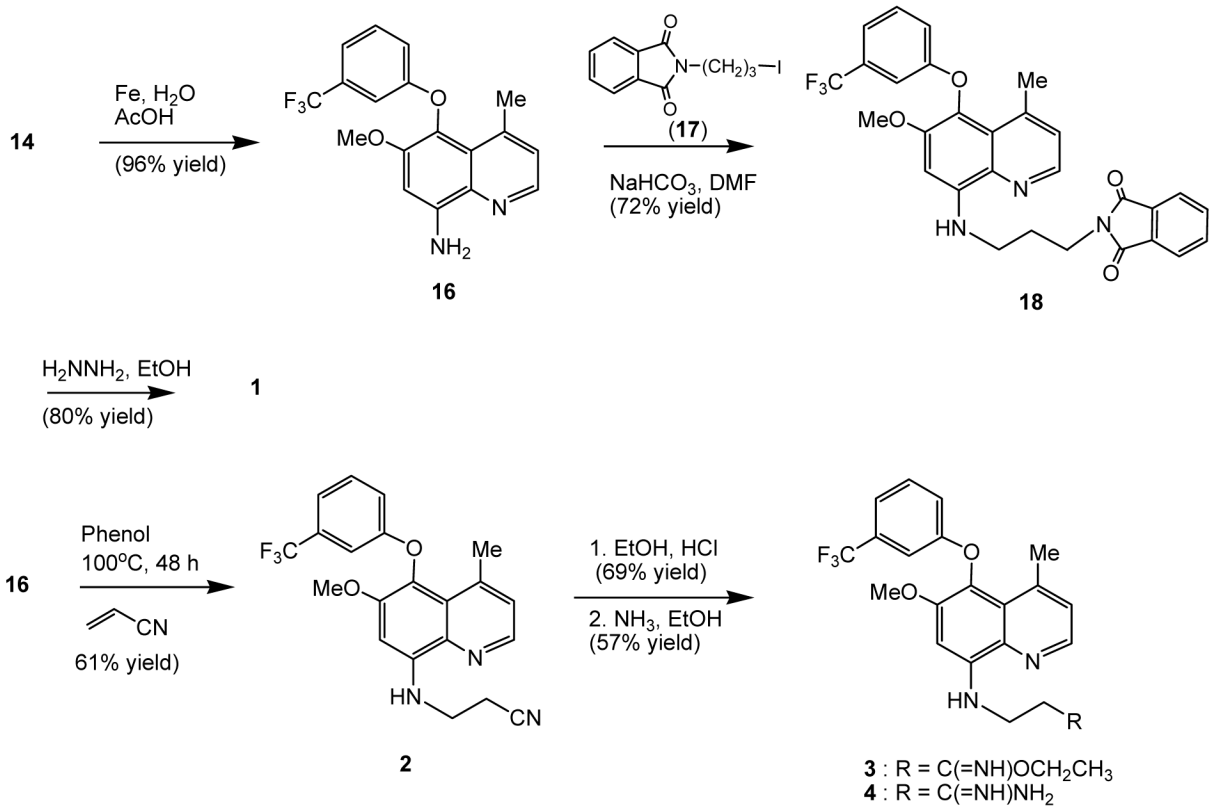

Scheme 3.
Synthesis of substituted quinolines **1 ~ 4**.

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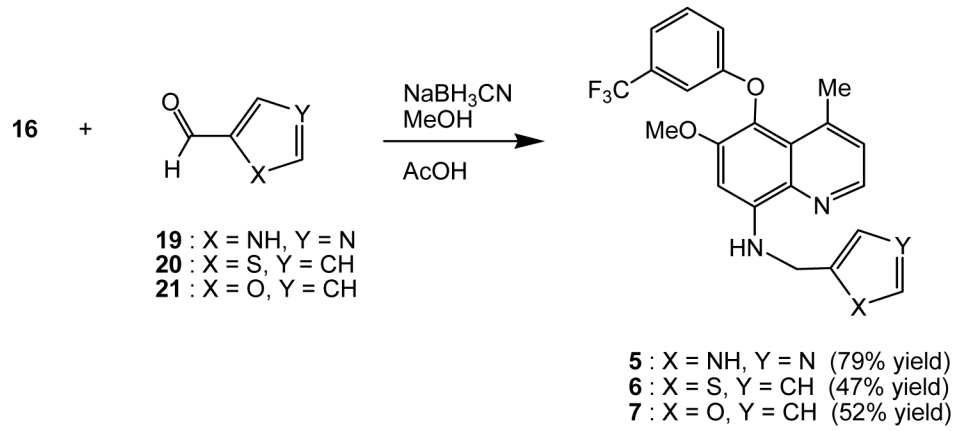

Scheme 4.
Synthesis of substituted quinolines **5** ~ **7**.

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Table 1

Cell Viability using Trypan Blue Exclusion. T47D breast cancer cells were treated with various concentrations of **1** – **7** for 2 days. A cell suspension was mixed with trypan blue dye and then visually examined to determine whether cells take up or exclude dye. The number of live cells (excluded dye) was quantified and IC_{50} value for each compound was determined.

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**
IC_{50} value (nM)	119 ± 21	378 ± 79	1974 ± 404	519 ± 102	1276 ± 246	3732 ± 696	15.6 ± 3.0