

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
ALVARO CORREA ORDOÑEZ

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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ASUNTO	Radicación	07-39071
	Trámite	011
	Evento	378
	Actuación	430
	Oficio	
	Folios	011

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Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (Fase Nacional)	☒	Cap. I	☒ Cap. II ☐

No. Sol. Internacional	<u>PCT/US2005/037839</u>
Fecha de Presentación Internacional	<u>21/10/2005</u>

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios 31 a 62 como se radicó inicialmente.

Reivindicaciones: Folios 63 a 69 modificado.

Prioridad: Folio 1 US 60/621,280 del 22/10/2004.

2. Objeto de la invención

Título: 4-[(2,4-DICLORO-5-METOXIFENIL)AMINO]-6-ALCOXI-7-ETINIL-3-QUINOLINOCARBONITRILOS PARA EL TRATAMIENTO DE LESIÓN ISQUÉMICA.

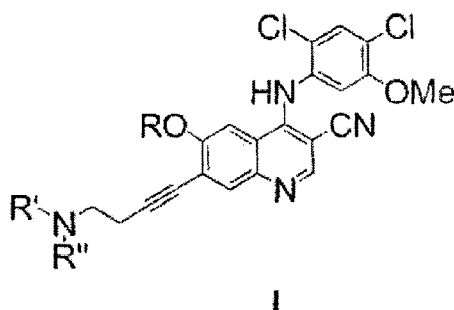
Objeto: La invención consiste en compuestos derivados de 3-ciano-4-aminoquinolina de fórmula (I) como inhibidores de la Src-quinasa y sus composiciones farmacéuticas.

El problema planteado es la necesidad de proveer nuevos compuestos inhibidores de la Src-quinasa que presenten mejores propiedades que los ya conocidos y sean útiles para trastornos de la permeabilidad vascular.

Para solucionar este problema técnico la solicitud proporciona compuestos derivados de 3-ciano-4-aminoquinolina fórmula (I) y sus composiciones farmacéuticas.

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Reivindicaciones 1 a 6: Compuestos de fórmula (I)



Reivindicaciones 7 a 9: Composiciones farmacéuticas que comprenden un compuesto de fórmula (I) junto con portadores aceptables.

Reivindicaciones 10 a 21: Métodos para suministrar neuroprotección.

Reivindicaciones 22 a 27: Uso de los compuestos de fórmula (I)

Se catalogó la invención según la IPC así: C07D 215/44, A61K 31/4706 y A61P 9/10.

3. Excepción a la patentabilidad (artículo 20 D 486 literal a)-d))

Las reivindicaciones 10 a 21 se refieren a métodos para suministrar neuroprotección, lo cual no es patentable de acuerdo a este artículo.

4. Reivindicaciones relativas a uso o a uso distinto (artículos 14 y 21 D 486)

Las reivindicaciones 22 a 27 indican el uso de los compuestos de fórmula (I), lo cual no se considera como invención y por lo tanto no es patentable.

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 22/10/2004, se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Nº	Documento	Título	Fecha de publicación
D1	WO 0475898	4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-alkoxy-3-quinolinecarbonitriles for the treatment of ischemic injury	10/09/2004
D2	Publicación*	Synthesis and inhibition of Src kinase activity by 7-ethenyl and 7-ethynyl-4-anilino-3-quinolinecarbonitriles	09/02/2004

* Bioorganic & Medicinal Chemistry Letters 14 (2004) 2155–2158

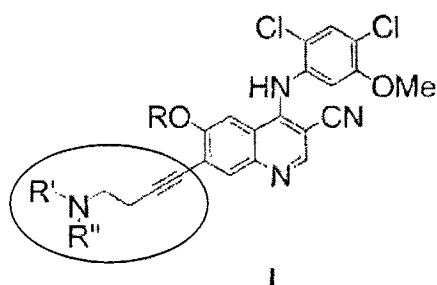
6. Análisis de patentabilidad (artículo 14 D 486)

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial para establecer la patentabilidad de la invención reivindicada en la solicitud

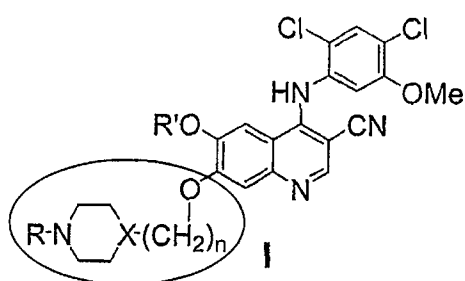
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Nivel Inventivo: (artículo 18 D 486)

La reivindicación 1 reclama compuestos derivados de 3-ciano-4-(2,4-dicloro-5-metoxifenil)-amino quinolina de fórmula (I) con actividad inhibidora de la Src-quinasa.



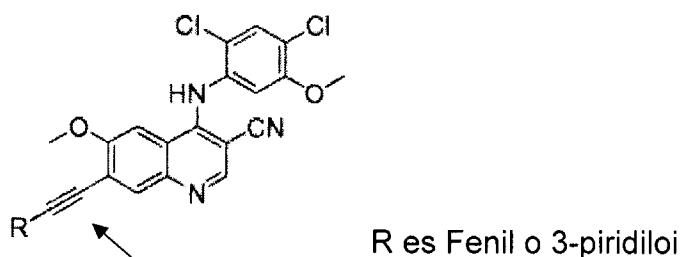
El documento D1 describe compuestos derivados de 3-ciano-4-amino-quinolina y sus procesos de síntesis (página 3) como inhibidores de la Src-quinasa de fórmula:



La única diferencia entre los compuestos de la solicitud y los divulgados en D1 es el sustituyente etinil de la posición 7 (recuadro). El efecto dado por esta diferencia, en teoría, es un aumento en la potencia y una mayor selectividad por la enzima Src, sin embargo dicho efecto no está sustentado por los datos de los ensayos de actividad indicados en la descripción (CI_{50} entre 1 nM y 10 nM).

De acuerdo a D1, la actividad inhibidora de la Src-quinasa de los compuestos allí mencionados está dada en gran medida por el núcleo de 3-ciano-4-(2,4-dicloro-5-metoxifenil)-amino quinolina y allí se plantea las rutas sintéticas para obtener derivados 7-sustituídos de dicho núcleo (página 3).

El documento D2 menciona derivados de 3-ciano-4-(2,4-dicloro-5-metoxifenil)-amino quinolina de fórmula (tabla 1):



Como se puede apreciar D2 sugiere la inclusión de un grupo etinil sustituido en la posición 7 del núcleo de 3-ciano-4-(2,4-dicloro-5-metoxifenil)-amino quinolina manteniendo así las propiedades inhibidoras Src-quinasa.

Así las cosas, vemos que la única diferencia estructural de los compuestos de la solicitud con respecto a D1, está claramente sugerida en D2 y aún así, no le conceden a los compuestos reivindicados un efecto técnico inesperado o ventaja con respecto a los presentes en el estado de la técnica si se tienen en cuenta los datos de actividad obtenidos en el ensayo con la enzima Src (ver datos de CI_{50} tabla 1 pág 12 de D1 y tabla 1 pág 2157 de D2 vs folio 40 de la solicitud).

Dado que D1 divulgaba derivados de 3-ciano-4-(2,4-dicloro-5-metoxifenil)-amino quinolina con propiedades inhibitorias de la Src-quinasa, el técnico medio, enfrentado al problema de encontrar compuestos con esta actividad, encuentra en D1 derivados de 3-cianoquinolina y sus procesos de síntesis y de acuerdo a las enseñanzas de D2 incluiría un sustituyente etinil en la posición 7 del anillo para obtener así compuestos que no ostentan ningún efecto técnico sorprendente o inesperado, por lo tanto los compuestos reclamados se derivan de manera evidente de las enseñanzas de D1 y D2, razón por la cual no cumplen con el requisito de nivel inventivo.

7. Conclusión

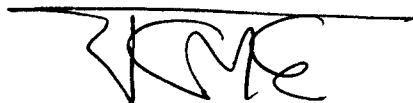
Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO 0475898	1 a 9	Nivel Inventivo
D2	Publicación*	1 a 9	Nivel Inventivo

* Bioorganic & Medicinal Chemistry Letters 14 (2004) 2155–2158

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.



JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha 12 9 DIC 2010.

CONCEPTO TECNICO No. 4097	EXAMINADOR TECNICO Código No. 202077
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EXP 2007 039071

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(71) Applicant (for all designated States except US): **WYETH**
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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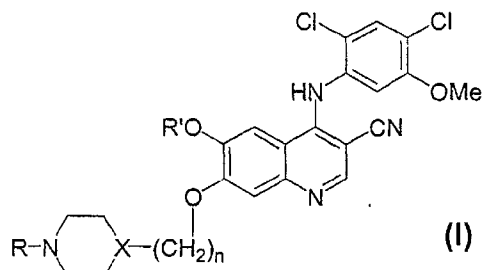
- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2004/075898 A1

(54) Title: 4-[(2,4-DICHLORO-5-METHOXYPHENYL)AMINO]-6-ALKOXY-3-QUINOLINECARBONITRILES FOR THE TREATMENT OF ISCHEMIC INJURY



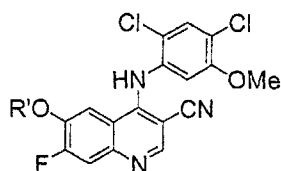
(57) Abstract: Compounds of the Formula (I), wherein X is N, CH n is an integer from 1-3; and R' and R are independently, alkyl of 1 to 3 carbon atoms, and pharmaceutically acceptable salts thereof, with the proviso that when n is 1, X is not N; are useful for inhibiting vascular permeability caused by disease, injury, or other trauma.

- 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-[(1-ethylpiperidin-4-yl)methoxy]-6-methoxyquinoline-3-carbonitrile;
- 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-methylpiperazin-1-yl)-propoxy]quinoline-3-carbonitrile;
- 5 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[(1-methylpiperidin-4-yl)-methoxy]quinoline-3-carbonitrile;
- 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-ethylpiperazin-1-yl)-propoxy]quinoline-3-carbonitrile;
- 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(1-methylpiperidin-4-yl)-propoxy]quinoline-3-carbonitrile;
- 10 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(4-methyl-1-piperazinyl)-ethoxy]quinoline-3-carbonitrile;
- 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(1-methylpiperidin-4-yl)-ethoxy]quinoline-3-carbonitrile; and
- 15 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-propyl-1-piperazinyl)-propoxy]-3-quinolinecarbonitrile; and pharmaceutically acceptable salts thereof.

Also provided is a process for the preparation of compounds of formula I wherein X is CH and all other groups are as defined above, comprising:

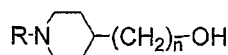
20

(a) reacting a quinoline of formula



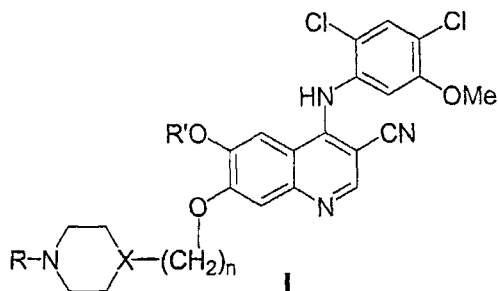
wherein R' is as defined herein, with an alcohol of formula

25



wherein R and n are as defined above, optionally in the presence of a base, e.g. sodium hydride or sodium,

Table 1. Inhibition of Src enzymatic and cellular activity



Example	X	R	n	R'	Src enzyme	Src cells
					IC ₅₀ nM	IC ₅₀ nM
1	N	Me	3	Me	1.2	100
2	N	Et	3	Me	0.77	130
3	N	Me	2	Me	4.0	380
4	N	Et	2	Me	3.6	600
5	CH	Me	1	Me	2.0	320
6	CH	Me	2	Me	1.9	210
7	CH	Me	3	Me	1.4	100
8	CH	Et	1	Me	2.1	170
9	N	Me	3	Et	NT	86
10	CH	Me	1	Et	2.1	176
11	N	Et	3	Et	0.85	160
12	CH	Me	3	Et	1.4	96
13	N	Me	2	Et	1.5	146
14	CH	Me	2	Et	1.9	267
15	N	n-Pr	3	Me	1.1	160

IP administration of Example 1 provides neuroprotection in transient model of focal ischemia

Example 1 was tested in a rat model of transient focal ischemia. Wistar rats were subjected to a 90 min occlusion of the middle cerebral artery (MCA) using an intraluminal suture approach as described by Longa *et al.*, *Stroke* 1989, 20:84 followed by reperfusion for 48 hours. Eighty-five minutes after the initial onset of ischemia, animals received compound of Example 1 (1.5, 5, 15, or 45 mg/kg ip).



Synthesis and inhibition of Src kinase activity by 7-ethenyl and 7-ethynyl-4-anilino-3-quinolinecarbonitriles

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Abstract—A series of 7-ethynyl and 7-ethenyl-4-anilino-3-quinolinecarbonitriles were synthesized and tested for Src inhibition. Derivatives bearing a C-6 methoxy group and 2,4-dichloro-5-methoxyaniline at C-4 showed optimal inhibition of Src enzymatic and cellular activity. The ethenyl and ethynyl groups were incorporated at C-7 utilizing a Stille, Heck, or Sonogashira coupling reaction.

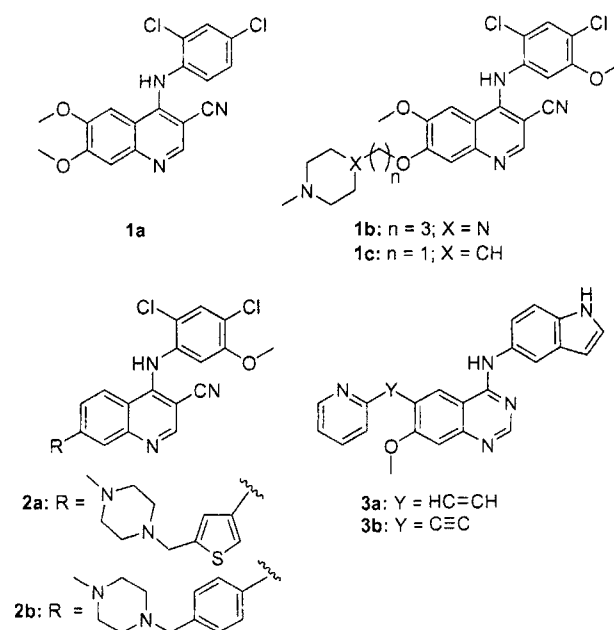
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Protein tyrosine kinases constitute approximately 20% of known and predicted protein kinases. These enzymes play a central role in signal transduction and cellular mechanisms.¹ Src, a nonreceptor tyrosine kinase, is the founding member of a group of structurally homologous proteins referred to as the Src family of kinases (SFKs). Elevated Src activity/expression has been associated with several disease states including cancer and osteoporosis.² As a result, Src has been recognized as an important therapeutic target and several classes of inhibitors have been synthesized.³

In earlier work we identified 4-anilino-6,7-dialkoxy-3-quinolinecarbonitrile **1a** as an ATP competitive inhibitor of Src kinase activity, with no significant inhibition against other kinases, including EGFR, FGFR, and Cdk4.⁴ After optimization of the substituents at C-4 and C-7, superior Src inhibitory activity was seen with derivatives **1b**⁵ and **1c**,⁶ which bear a 2,4-dichloro-5-methoxy aniline group at C-4 and a 3-(4-methyl-1-piperazinyl)-propoxy or 1-methylpiperidinemethoxy substituent at C-7, respectively.

We have also shown that groups other than alkoxy are tolerated at C-7.⁷ For example, 7-thienyl and 7-

phenyl derivatives **2a** and **2b** constitute potent Src inhibitors.



Keywords: Src kinase; Src inhibitors; Kinase inhibitors; Tyrosine kinase; Quinolinecarbonitriles.

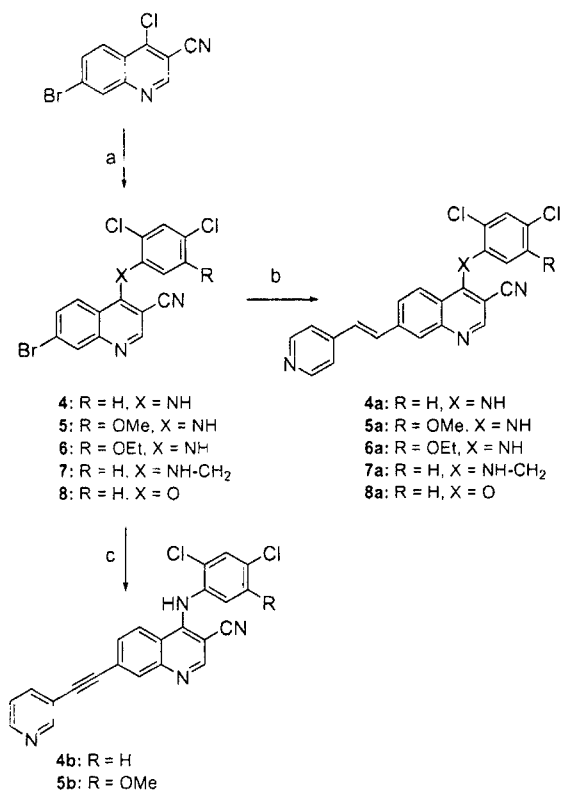
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Interestingly, related 4-heteroaryl-6-ethenyl quinazolines and their 6-ethynyl derivatives (**3a**, **3b**) have been

claimed to be EGFr inhibitors.⁸ As part of our ongoing investigations, we sought to introduce an ethenyl or ethynyl group at C-7 of the 3-quinolinecarbonitrile.

We began our synthetic studies by reacting the previously reported intermediate 7-bromo-4-chloro-3-quinolinecarbonitrile^{7a} with 2,4- and 2,4,5-substituted anilines, 2,4-dichlorobenzylamine, and 2,4-dichlorophenol to give the 4-substituted derivatives **4–8** (Scheme 1). Subsequent treatment of **4–8** with 4-vinylpyridine under Heck coupling conditions provided C-7 ethenyl derivatives **4a–8a**. Similarly, treatment of intermediates **4** and **5**^{7a} with 3-ethynylpyridine under Sonogashira coupling conditions yielded C-7 ethynyl derivatives **4b** and **5b**.

As previously observed with the 7-alkoxy, 7-thienyl, and 7-phenyl series, 2,4-dichloro-5-methoxy aniline (**5a**) was found to be the preferred aniline for Src inhibition (Table 1). Although removal of the aniline C-5 methoxy substituent (**4a**) resulted in a decrease in inhibitory activity, replacement of this group with an ethoxy substituent (**6a**) was more detrimental. Similarly, extending the C-4 NH linker of **4a** with a methylene group (**7a**) or replacing it with an oxygen (**8a**) decreased the Src inhibitory activity 24- and 9-fold, respectively, in the enzyme assay. Loss of activity was also observed in the Src-dependent cell proliferation assay.



Scheme 1. Reagents and conditions: (a) aniline, pyridine hydrochloride or NaH; benzylamine, Hünigs base/DMF; phenol, K₂CO₃/DMF; (b) 4-vinylpyridine, Pd(OAc)₂, P(*o*-Tol)₃, DMF, TEA; (c) 3-ethynylpyridine, Pd(Ph)₃Cl, CuI, DMF, TEA.

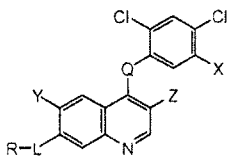
We then studied the effect of replacing the 3-cyano substituent with an ester (**12**) or acid group (**13**). For the synthesis of these derivatives, ethyl 7-bromo-1,4-dihydro-4-oxo-3-quinolinecarboxylate **9**, synthesized by a known route,⁹ was treated with phosphorous oxychloride to give ethyl 7-bromo-4-chloro-3-quinolinecarboxylate **10** (Scheme 2). Reaction of **10** with 2,4-dichloroaniline using pyridine hydrochloride gave intermediate **11**. Heck coupling reaction of **11** with 4-vinylpyridine provided ethyl 3-quinolinecarboxylate **12**, which was hydrolyzed to give carboxylic acid **13**. Derivatives **12** and **13** showed no significant Src inhibitory activity, implying that the 3-cyano group is required for good Src inhibition.

Following the synthesis of derivatives with varying groups at C-3, we proceeded to replace the pyridine ring linked to C-7, with other aryl or heteroaryl groups. As shown in Scheme 3, intermediate **5**^{7a} was reacted with several ethenyl¹⁰ and ethynyl reagents under Heck and Sonogashira coupling conditions, respectively. For the synthesis of the unsubstituted vinyl derivative **14**, **5** was reacted with tributyl(vinyl)tin under Suzuki conditions. Ethyl derivative **24** was synthesized by treatment of **23** with Pd/C under a hydrogen atmosphere.

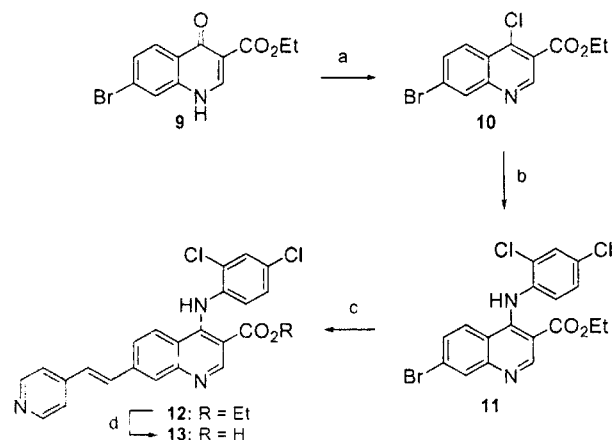
Of the different aryl and heteroaryl groups tested in the 7-ethenyl series, 3- and 4-ethynylpyridine derivatives **19** and **5a** showed superior Src inhibitory activity. Although the IC₅₀ value obtained for 2-ethynylpyridine **18** in an enzyme assay did not differ significantly from the values found for **19** and **5a**, compound **18** was much less potent in a cell proliferation assay. In contrast to the ethenyl series, in the C-7 ethynyl series, 3-ethynylpyridine **5b** was found to inhibit Src-dependent cell proliferation with an IC₅₀ value of 0.65 μM, while the 4-ethynylpyridine **23** had an IC₅₀ of only 2.7 μM and the IC₅₀ for the 2-ethynylpyridine **22** was >10 μM. The IC₅₀ values obtained from the enzyme assay showed a similar correlation. Saturation of the ethynyl linker (**24**) resulted in a large decrease in Src inhibition.

Finally, we investigated the importance of having an alkoxy substituent at C-6. Previous studies on 6,7-dialkoxy-3-quinolinecarbonitriles showed that the presence of a small alkoxy group at C-6, like OMe, generally improved Src inhibitory activity.⁶ Interestingly, the opposite is true for the 7-phenyl series,^{7b} where the best Src inhibition was observed when C-6 was unsubstituted. As shown in Scheme 4, known intermediate 4-chloro-3-cyano-6-methoxy-7-quinolinyl-trifluoromethanesulfonate was prepared as previously reported.^{7b} 6-Methoxy-7-ethenyl derivatives **25–27** and 6-methoxy-7-ethynyl derivatives **28** and **29** were prepared as previously described. As observed for the 6,7-dialkoxy-3-quinolinecarbonitrile series, the presence of a methoxy group at C-6 improved Src inhibition, in most cases, more than 2-fold. 4-Ethenylpyridine derivative **27** exhibited an improved IC₅₀ value of 0.08 μM in the Src dependent cell assay and of 4.2 nM in the enzyme assay, compared to its C-6 unsubstituted derivative **5a**, which exhibited IC₅₀ values of 0.23 μM and 9.9 nM, respectively.

Table 1.

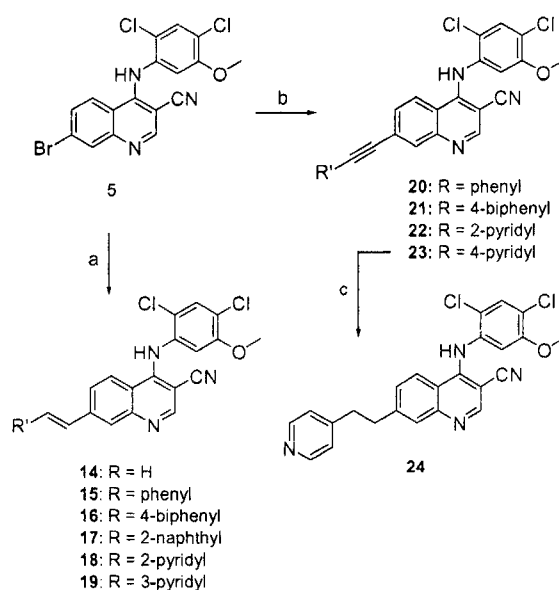


Compound ¹¹	R	L	Y	X	Q	Z	Src enzyme ¹² IC ₅₀ nM (SD)	Src cells ¹³ IC ₅₀ μM (SD)
1b	—	—	—	—	—	—	3.6	0.10
4a	4-Pyridyl	Ethenyl	H	H	NH	CN	42 (6.0)	1.2 (0.13)
4b	3-Pyridyl	Ethynyl	H	H	NH	CN	200 (49)	3.9 (0.049)
5a	4-Pyridyl	Ethenyl	H	OMe	NH	CN	9.9 (2.9)	0.23 (0.10)
5b	3-Pyridyl	Ethynyl	H	OMe	NH	CN	47 (11)	0.65 (0.093)
6a	4-Pyridyl	Ethenyl	H	OEt	NH	CN	3100 (610)	>10 (n = 2)
7a	4-Pyridyl	Ethenyl	H	H	NHCH ₂	CN	1000 (180)	>10 (n = 2)
8a	4-Pyridyl	Ethenyl	H	H	O	CN	380 (23)	7.2 (2.3)
12	4-Pyridyl	Ethenyl	H	H	NH	CO ₂ Et	12,000 (4300)	>10 (n = 2)
13	4-Pyridyl	Ethenyl	H	H	NH	CO ₂ H	1600 (200)	>10 (n = 2)
14	H	Ethenyl	H	OMe	NH	CN	97 (28)	9.3 (3.2)
15	Phenyl	Ethenyl	H	OMe	NH	CN	180 (9.8)	2.7 (0.98)
16	4-Biphenyl	Ethenyl	H	OMe	NH	CN	2300 (500)	>10 (n = 2)
17	2-Naphthyl	Ethenyl	H	OMe	NH	CN	320 (86)	>10 (n = 2)
18	2-Pyridyl	Ethenyl	H	OMe	NH	CN	19 (2.8)	50% inhibition at 10 μM (22%)
19	3-Pyridyl	Ethenyl	H	OMe	NH	CN	15 (1.6)	0.23 (0.003)
20	Phenyl	Ethynyl	H	OMe	NH	CN	320 (48)	>10 (n = 2)
21	4-Biphenyl	Ethynyl	H	OMe	NH	CN	420 (31)	>10 (n = 2)
22	2-Pyridyl	Ethynyl	H	OMe	NH	CN	530 (81)	>10 (n = 2)
23	4-Pyridyl	Ethynyl	H	OMe	NH	CN	83 (12)	2.7 (1.0)
24	4-Pyridyl	Ethylene	H	OMe	NH	CN	440 (53)	>10 (n = 2)
25	Phenyl	Ethenyl	OMe	OMe	NH	CN	65 (20)	1.5 (0.16)
26	3-Pyridyl	Ethenyl	OMe	OMe	NH	CN	8.4 (2.6)	0.14 (0.051)
27	4-Pyridyl	Ethenyl	OMe	OMe	NH	CN	4.2 (0.7)	0.08 (0.006)
28	Phenyl	Ethynyl	OMe	OMe	NH	CN	57 (14)	3.0 (0.87)
29	3-Pyridyl	Ethynyl	OMe	OMe	NH	CN	12 (4.2)	0.27 (0.033)

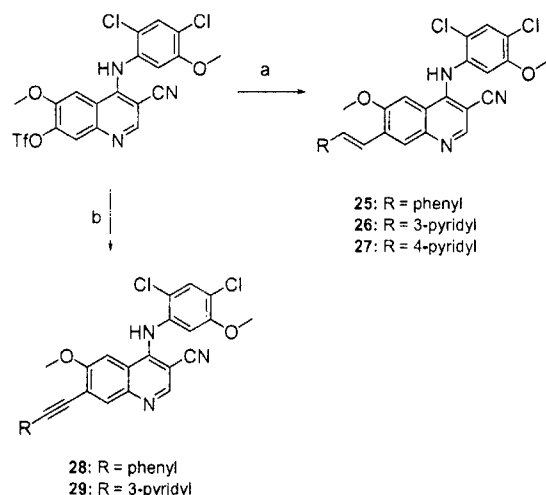


Scheme 2. Reagents and conditions: (a) phosphorous oxychloride, DMF; (b) 2,4-dichloroaniline, pyridine hydrochloride; (c) 4-vinylpyridine, Pd(OAc)₂, P(*o*-Tol)₃, DMF, TEA; (d) NaOH.

With these studies we have shown that 3-quinolinecarbonitriles bearing ethynylpyridine and ethenylpyridine groups at C-7 represent potent Src inhibitors. Analogous to the results observed with the 6,7-dialkoxy-3-quinolinecarbonitrile series, the preferred group at C-4 was



Scheme 3. Reagents and conditions: (a) alkene, Pd(OAc)₂, P(*o*-Tol)₃, DMF, TEA; (b) alkyne, Pd(Ph₃P)₄, CuI, DMF, TEA; (c) Pd/C, MeOH, H₂.



Scheme 4. Reagents and conditions: (a) alkene, Pd(OAc)₂, P(*o*-Tol)₃, DMF, TEA; (b) alkyne, Pd(Ph₃P)₄, CuI, DMF, TEA.

2,4-dichloro-5-methoxyaniline. Substituting C-6 with a methoxy group resulted in an increase in Src inhibition. Derivative **27** was the most potent inhibitor in this series, showing comparable activity to **1b** in both the Src enzyme and Src-dependent cell proliferation assays. We are continuing to investigate the physicochemical and biological properties of these analogs and other related compounds. The results will be reported in due time.

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References and notes

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- Noncommercial 3-vinylpyridine was synthesized by reaction of 3-iodopyridine with tributyl(vinyl)tin under Suzuki conditions.
- All compounds were characterized by MS, NMR, and CHN combustion analysis.
- The IC₅₀ values reported represent the means of at least 2 determinations. The standard deviations (SD) are shown in the brackets. *Src kinase assay*: Recombinant human Src enzyme was obtained from PanVera (P3044). Biotinylated peptide corresponding to residues 6–20 of Cdk1 was used as a substrate (Biotin-KVEKIGEGTYGVVYK-COOH). Homogeneous fluorescence resonance energy transfer kinase assays were performed using the europium/APC detection format (LANCER, Perkin Elmer). Src enzyme (10 ng) was mixed with biotinylated peptide (final concentration 2 μM), 50 mM Hepes (pH 7.5), 10 mM MgCl₂, 20 μg/mL BSA, 0.001% Brij-35 (Sigma), 100 μM ATP, 1% DMSO. The kinase reaction was incubated for 70 min at 37°C. The reaction was stopped with EDTA at a final concentration of 30 mM EDTA/25 mM Hepes (pH 7.5)/10 μg/mL BSA. The mixture was combined with Eu-labeled anti-phosphotyrosine antibody PT66 (Perkin Elmer, AD0068) and Streptavidin Surelight-APC (Perkin Elmer, CR130-100) in 50 mM Hepes (pH 7.5)/20 μg/mL BSA, and incubated for 30 min according to manufacturer's specifications. Fluorescence intensity at 665 nm was used to monitor the extent of the kinase reaction. It should be noted that the Src enzyme assay used here is different from the ELISA assay used in our previous publications (Refs. 4–7).
- Compounds were tested according to the Src cellular assay reported previously.⁴