

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

2020  
Bogotá, D.C.,

Abogado  
**Emilio Ferrero**  
Apoderado

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



**No. 07-031445- -00006-0000**

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| ASUNTO | Radicación | 07 31445 |
|        | Trámite    | 002      |
|        | Evento     | 001      |
|        | Actuación  | 430      |
|        | Oficio     | 013      |
|        | Folios     | 013      |

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap.I ☒ Cap. II ☐

No. Sol. Internacional PCT/EP2005/010119  
Fecha de Presentación Internal. 20/09/05

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**

- 1.1. Descripción: Folios 57 - 96
- 1.2. Reivindicaciones: Folios 124 - 128
- 1.3. Prioridad: Presentada en Europa, el 29.09.04, bajo el número 04023130.0

**2. Objeto de la invención**

- Título de la solicitud: "Forma termodinámica estable de una sal tosionato"

Según las reivindicaciones 1-25 se refiere al polimorfo (I) de sorafenib y composiciones farmacéuticas que los contienen.

El problema planteado en esta solicitud es la necesidad de un polimorfo más estable de sorafenib.

Para solucionar este problema técnico la solicitud en estudio proporciona los polimorfos de la presente solicitud

- Clasificación Internacional de Patentes A 61 K 31/44

**3. Reivindicaciones de Uso (artículo 14 D 486)**

El contenido de las reivindicaciones 10-11, que trata de “Uso del compuesto...”, no es patentable, debido a que se la legislación vigente únicamente contempla los productos y procedimientos como objeto de ser patentados.

**4. 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 17.09.04, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

| Nº | Documento  | Título                                                                  | Fecha de Publicación |
|----|------------|-------------------------------------------------------------------------|----------------------|
| D1 | WO 0042012 | “Difenil ureas carboxiaril sustituidas como inhibidores de quinasa RAF” | 20.07.00             |
| D2 |            | “Remington Farmacia”                                                    | 1995                 |

**5. Análisis de patentabilidad (artículo 14 D486)**

5.1. Nivel Inventivo (artículo 18 D486)

5.2.

- El documento WO 0042012 enseña el compuesto sorafenib tosilato en su forma polimórfica (II)
- El libro de texto “Remington Farmacia”, en su capítulo de predformulación, enseña que el fenómeno del polimorfismo es bien difundido en sustancias de interés farmacéutico y que es obligación del preformulador encontrar y estudiar todas las formas polimórficas de un compuesto con el fin de usar la forma polimórfica más adecuada para adaptarlas a formulaciones farmacéuticas, debido a que diferentes formas polimórficas de un mismo activo presentan propiedades fisicoquímicas diferentes, tales como solubilidad, estabilidad, etc.

Teniendo en cuenta el objeto de la presente solicitud, el cual es proveer más formas polimórficas de sorafenib , es una derivación evidente del estado de la técnica, debido a que un técnico medio estaría en capacidad de tomar el polimorfo de D1 y mediante sus conocimientos usuales en formulación (reflejados en D2), proceder a obtener más formas polimórficas de sorafenib

con la expectativa de que fueran más estables y adecuadas para ser incluidas en formas farmacéuticas.

Finalmente no se revela un efecto sorprendente o mejorado de las formas polimórficas que se reivindican en comparación con lo conocido en el estado de la técnica.

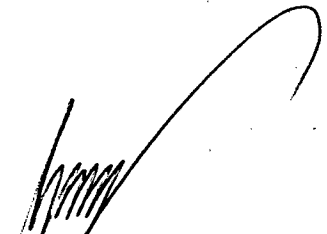
6. Conclusión:

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

| Nº | Documento            | Reivindicaciones Afectadas | Requisito que Afecta |
|----|----------------------|----------------------------|----------------------|
| D1 | WO 0042012           | 1-9, 12-25                 | Nivel Inventivo      |
|    |                      |                            |                      |
| D2 | "Remington Farmacia" | 1-9, 12-25                 | Nivel Inventivo      |
|    |                      |                            |                      |

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 5 del título primero de la Circular Única N° 10 de 2001.

  
**Álix Carmenza Céspedes de Vergel**  
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha \_\_\_\_\_

|                                     |                                               |
|-------------------------------------|-----------------------------------------------|
| <b>CONCEPTO TÉCNICO No.</b><br>2946 | <b>EXAMINADOR TÉCNICO</b><br>Código No.202024 |
|-------------------------------------|-----------------------------------------------|

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (51) International Patent Classification <sup>7</sup> :<br><b>C07D 211/78, 211/72, A61K 31/33,<br/>31/54, 31/535, 31/17, C07C 275/20,<br/>275/22, 275/24, 275/28</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  | A1 | (11) International Publication Number: <b>WO 00/42012</b><br><br>(43) International Publication Date: 20 July 2000 (20.07.00)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| (21) International Application Number: PCT/US00/00648<br>(22) International Filing Date: 12 January 2000 (12.01.00)<br><br>(30) Priority Data:<br>60/115,877 13 January 1999 (13.01.99) US<br>09/257,266 25 February 1999 (25.02.99) US<br>09/425,228 22 October 1999 (22.10.99) US<br><br>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications<br>US 60/115,877 (CIP)<br>Filed on 13 January 1999 (13.01.99)<br>US 09/257,266 (CIP)<br>Filed on 25 February 1999 (25.02.99)<br>US 09/425,228 (CIP)<br>Filed on 22 October 1999 (22.10.99)<br><br>(71) Applicant (for all designated States except US): BAYER CORPORATION [US/US]; 100 Bayer Road, Pittsburgh, PA 15205 (US). |  |    | (72) Inventors; and<br>(75) Inventors/Applicants (for US only): RIEDL, Bernd [DE/DE]; Von-der-Glotz-Strasse 7, D-42329 Wuppertal (DE). DU-MAS, Jacques [FR/US]; 821 Beechwood Road, Orange, CT 06477 (US). KHIRI, Uday [IN/US]; 101 Tanglewood Drive, Hamden, CT 06518 (US). LOWINGER, Timothy, B. [CA/JP]; # 203, 5-7, Chitose-Cho, Nishinomiya City, Hyogo 662-0046 (JP). SCOTT, William, J. [US/US]; 210 Saddle Hill Drive, Guilford, CT 06437 (US). SMITH, Roger, A. [CA/US]; 65 Winterhill Road, Madison, CT 06443 (US). WOOD, Jill, E. [US/US]; 72 Pickwick Road, Hamden, CT 06517 (US). MONAHAN, Mary-Katherine [US/US]; 134 Park Avenue, Hamden, CT 06517 (US). NATERO, Reina [US/US]; 113 Edgcomb Street, Hamden, CT 06518 (US). RENICK, Joel [US/US]; 11 Wall Street #4, Milford, CT 06460 (US). SIBLEY, Robert, N. [US/US]; 1187 Mt. Carmel Avenue, North Haven, CT 06473 (US).<br><br>(74) Agents: TRAVERSO, Richard, J. et al.; Millen, White, Zelano & Branigan, P.C., Arlington Courthouse Plaza 1, Suite 1400, 2200 Clarendon Boulevard, Arlington, VA 22201 (US).<br><br>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).<br><br>Published<br><i>With international search report.<br/>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| (54) Title: $\omega$ -CARBOXYARYL SUBSTITUTED DIPHENYL UREAS AS RAF KINASE INHIBITORS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| (57) Abstract<br><br>This invention relates to the use of a group of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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The term "cycloalkyl", as used herein, refers to cyclic structures with or without alkyl substituents such that, for example, "C<sub>4</sub> cycloalkyl" includes methyl substituted cyclopropyl groups as well as cyclobutyl groups. The term "cycloalkyl", as used herein also includes saturated heterocyclic groups.

5        Suitable halogen groups include F, Cl, Br, and/or I, from one to per-substitution (i.e. all H atoms on a group replaced by a halogen atom) being possible where an alkyl group is substituted by halogen, mixed substitution of halogen atom types also being possible on a given moiety.

The invention also relates to compounds *per se*, of formula I.

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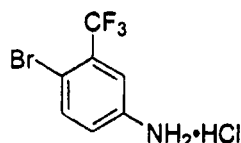
The present invention is also directed to pharmaceutically acceptable salts of formula I. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li<sup>+</sup> Na<sup>+</sup> or K<sup>+</sup>), alkaline earth cations (e.g., Mg<sup>+2</sup>, Ca<sup>+2</sup> or Ba<sup>+2</sup>), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic-substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, lysine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

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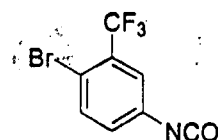
A number of the compounds of Formula I possess asymmetric carbons and can therefore exist in racemic and optically active forms. Methods of separation of enantiomeric and diastereomeric mixtures are well known to one skilled in the art. The present invention encompasses any isolated racemic or optically active form of compounds described in Formula I which possess raf inhibitory activity.

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**B. Synthesis of Urea Precursors****B1. General Method for the Synthesis of Isocyanates from Anilines Using CDI. Synthesis of 4-Bromo-3-(trifluoromethyl)phenyl Isocyanate.****5 Step 1. Synthesis of 4-bromo-3-(trifluoromethyl)aniline HCl salt**

To a solution of 4-bromo-3-(trifluoromethyl)aniline (64 g, 267 mmol) in Et<sub>2</sub>O (500 mL) was added an HCl solution (1 M in Et<sub>2</sub>O; 300 mL) dropwise and the resulting mixture was stirred at room temp. for 16 h. The resulting pink-white precipitate was removed by filtration and washed with Et<sub>2</sub>O (50 mL) and to afford 4-bromo-3-(trifluoromethyl)aniline HCl salt (73 g, 98%).

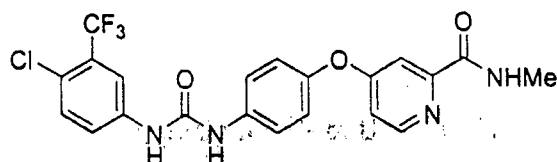
**Step 2. Synthesis of 4-bromo-3-(trifluoromethyl)phenyl isocyanate**

A suspension of 4-bromo-3-(trifluoromethyl)aniline HCl salt (36.8 g, 133 mmol) in toluene (278 mL) was treated with trichloromethyl chloroformate dropwise and the resulting mixture was heated at the reflux temp. for 18 h. The resulting mixture was concentrated under reduced pressure. The residue was treated with toluene (500 mL), then concentrated under reduced pressure. The residue was treated with CH<sub>2</sub>Cl<sub>2</sub> (500 mL), then concentrated under reduced pressure. The CH<sub>2</sub>Cl<sub>2</sub> treatment/concentration protocol was repeated and resulting amber oil was stored at -20 °C for 16 h, to afford 4-bromo-3-(trifluoromethyl)phenyl isocyanate as a tan solid (35.1 g, 86%); GC-MS *m/z* 265 (M<sup>+</sup>).

**C. Methods of Urea Formation**

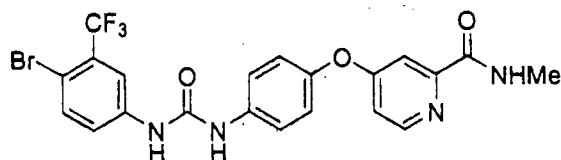
**C1a. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea**

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A solution of 4-chloro-3-(trifluoromethyl)phenyl isocyanate (14.60 g, 65.90 mmol) in  $\text{CH}_2\text{Cl}_2$  (35 mL) was added dropwise to a suspension of 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline (Method A2, Step 4; 16.0 g, 65.77 mmol) in  $\text{CH}_2\text{Cl}_2$  (35 mL) at 0 °C. The resulting mixture was stirred at room temp. for 22 h. The resulting yellow solids were removed by filtration, then washed with  $\text{CH}_2\text{Cl}_2$  (2 x 30 mL) and dried under reduced pressure (approximately 1 mmHg) to afford *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea as an off-white solid (28.5 g, 93%): mp 207-209 °C;  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$  2.77 (d,  $J=4.8$  Hz, 3H), 7.16 (m, 3H), 7.37 (d,  $J=2.5$  Hz, 1H), 7.62 (m, 4H), 8.11 (d,  $J=2.5$  Hz, 1H), 8.49 (d,  $J=5.5$  Hz, 1H), 8.77 (br d, 1H), 8.99 (s, 1H), 9.21 (s, 1H); HPLC ES-MS  $m/z$  465 ( $(\text{M}+\text{H})^+$ ).

**C1b. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of *N*-(4-Bromo-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea**



A solution of 4-bromo-3-(trifluoromethyl)phenyl isocyanate (Method B1, Step 2; 8.0 g, 30.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (80 mL) was added dropwise to a solution of 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline (Method A2, Step 4; 7.0 g, 28.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (40 mL) at 0 °C. The resulting mixture was stirred at room temp. for 16 h. The resulting yellow solids were removed by filtration, then washed with  $\text{CH}_2\text{Cl}_2$  (2 x 50 mL) and dried under reduced pressure (approximately 1 mmHg) at 40 °C to afford *N*-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea as a pale-yellow solid (13.2 g, 90%): mp 203-205 °C;  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$  2.77 (d,  $J=4.8$  Hz, 3H), 7.16 (m, 3H), 7.37 (d,  $J=2.5$  Hz, 1H), 7.58 (m, 3H), 7.77 (d,  $J=8.8$  Hz, 1H), 8.11 (d,  $J=2.5$  Hz, 1H), 8.49 (d,  $J=5.5$  Hz, 1H), 8.77 (br d, 1H), 8.99 (s, 1H), 9.21 (s, 1H); HPLC ES-MS  $m/z$  509 ( $(\text{M}+\text{H})^+$ ).

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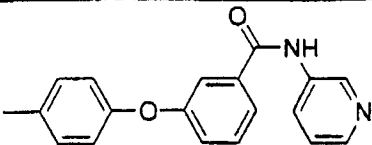
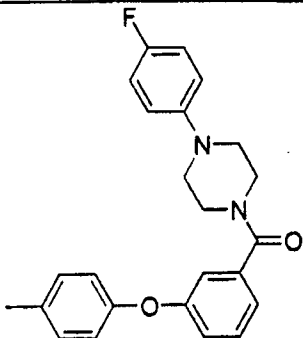
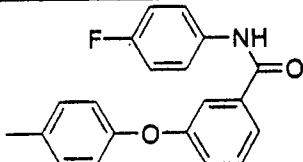
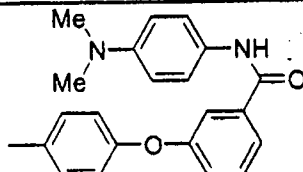
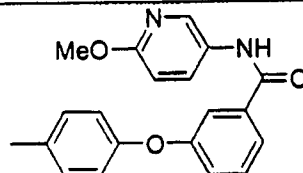
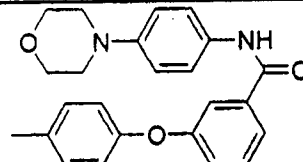
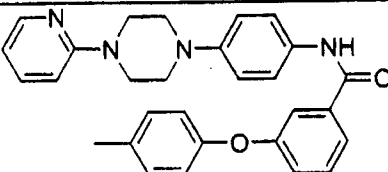
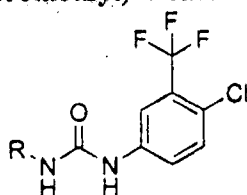
|    |                                                                                     |  |  |      |                                 |  |                         |
|----|-------------------------------------------------------------------------------------|--|--|------|---------------------------------|--|-------------------------|
| 34 |    |  |  | 0.11 | 70%<br>EtOAc<br>/ 30%<br>hexane |  | A11<br>B1<br>C1f<br>D1c |
| 35 |    |  |  | 0.38 | 70%<br>EtOAc<br>/ 30%<br>hexane |  | A11<br>B1<br>C1f<br>D1c |
| 36 |    |  |  | 0.77 | 70%<br>EtOAc<br>/ 30%<br>hexane |  | A11<br>B1<br>C1f<br>D1c |
| 37 |   |  |  | 0.58 | 70%<br>EtOAc<br>/ 30%<br>hexane |  | A11<br>B1<br>C1f<br>D1c |
| 38 |  |  |  | 0.58 | 70%<br>EtOAc<br>/ 30%<br>hexane |  | A11<br>B1<br>C1f<br>D1c |
| 39 |  |  |  | 0.17 | 70%<br>EtOAc<br>/ 30%<br>hexane |  | A11<br>B1<br>C1f<br>D1c |
| 40 |  |  |  | 0.21 | 70%<br>EtOAc<br>/ 30%<br>hexane |  | A11<br>B1<br>C1f<br>D1c |

Table 4. 3-(Trifluoromethyl)-4-chlorophenyl Ureas



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| Entry | R | mp<br>(°C) | HPLC<br>(min.) | TLC<br>R <sub>f</sub> | TLC<br>Solvent<br>System                | Mass<br>Spec.<br>[Source]     | Synth.<br>Method |
|-------|---|------------|----------------|-----------------------|-----------------------------------------|-------------------------------|------------------|
| 41    |   | 163-165    |                | 0.08                  | 50% EtOAc/<br>50% pet ether             | 464<br>(M+H)+<br>(HPLC ES-MS) | A13<br>C3        |
| 42    |   | 215        |                | 0.06                  | 50% EtOAc/<br>50% pet ether             | 465<br>(M+H)+<br>(HPLC ES-MS) | A2<br>C1a        |
| 43    |   |            |                | 0.10                  | 50% EtOAc/<br>50% pet ether             | 451<br>(M+H)+<br>(HPLC ES-MS) | A2<br>C1a        |
| 44    |   |            |                | 0.25                  | 30% EtOAc/<br>70% pet ether             | 451<br>(M+H)+<br>(HPLC ES-MS) | A2<br>C1a        |
| 45    |   |            |                | 0.31                  | 30% EtOAc/<br>70% pet ether             | 465<br>(M+H)+<br>(HPLC ES-MS) | A2<br>C1a        |
| 46    |   | 176-179    |                | 0.23                  | 40% EtOAc/<br>60% hexane                | 476<br>(M+H)+<br>(FAB)        | A3<br>C1a        |
| 47    |   |            |                | 0.29                  | 5% MeOH/<br>45% EtOAc/<br>50% pet ether | 478<br>(M+H)+<br>(HPLC ES-MS) | A5<br>C1c        |
| 48    |   | 206-209    |                |                       |                                         |                               | A15<br>C1a       |
| 49    |   | 147-151    |                | 0.22                  | 50% EtOAc/<br>50% pet ether             | 499<br>(M+H)+<br>(HPLC ES-MS) | A6<br>C1a        |
| 50    |   |            |                | 0.54                  | 100% EtOAc                              | 479<br>(M+H)+<br>(HPLC ES-MS) | A2<br>C1a        |