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What is known about this area of research?
Candidates help to make the best choice

Research Topic Candidates

<table>
<thead>
<tr>
<th>Research Topic Candidates</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>29 references were found containing &quot;tyrosine kinase inhibitors for treatment of cancer&quot;</td>
<td>29</td>
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<tr>
<td>closely associated with one another.</td>
<td>2245</td>
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<td>&quot;treatment&quot; and &quot;cancer&quot; were present anywhere in the reference.</td>
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<tr>
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<td>7912220 references were found containing the concept &quot;treatment&quot;.</td>
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<tr>
<td>3160974 references were found containing the concept &quot;cancer&quot;.</td>
<td>3160974</td>
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</tbody>
</table>

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1. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer
   By Fukuoka, Masahiro; Yano, Seiji; Giaccone, Giuseppe; Tamura, Tomohide; Nakagawa, Kazuhiko; Douillard, Jean-Yves; Nishiwaki, Yutaka; Vansteenkiste, Jchan; Kudch, Shinzoh; Rischin, Danny; et al
   From Journal of Clinical Oncology (2003), 21(12), 2237-2246. Language: English, Database: CAPLUS
   The aim was to evaluate the efficacy and tolerability of two doses of gefitinib (Iressa [ZD1839]; AstraZeneca, Wilmington, DE), a novel epidermal growth factor receptor tyrosine kinase inhibitor, in patients with pretreated advanced non-small-cell lung cancer (NSCLC). This was a randomized, double-blind, parallel-group, multicenter phase II trial. Two hundred ten patients with advanced NSCLC who were previously treated with one or two chemotherapy regimens (at least one contg. platinum) were randomized to receive either 250-mg or 500-mg oral doses of gefitinib once daily. Efficacy was simil...

2. ERBB receptors and cancer: the complexity of targeted inhibitors
   By Hynes, Nancy E.; Lane, Heidi A.
   A review. ERBB receptor tyrosine kinases have important roles in human cancer. In particular, the expression or activation of epidermal growth factor receptor and ERBB2 are altered in many epithelial tumors, and clin. studies indicate that they have important roles in tumor etiol. and progression. Accordingly, these receptors have been intensely studied to understand their importance in cancer boll. and as therapeutic targets, and many ERBB inhibitors are now used in the clinic. We will discuss the significance of these receptors as clin. targets, in particular the mol. mechanisms underlying response.
4. Preparation of quinazolinyloxy spiroheterocycles as tyrosine kinase inhibitors.

By: Hmelsbach, Frank; Jung, Birgit; Lotz, Ralf
Assignee: Boehringer Ingelheim International GmbH, Germany

Title comps. [I; R1 = (substituted) Ph, 1-phenethyl; R2 = H, (substituted) alkyl, cycloalkyl, cycloalkylalkyl; R3 = H, (substituted) alkyl, cycloalkyl, cycloalkylalkyl, alkylcarbonyl, cycloalkylcarbonyl, alkylsulfonyl, PhCO, PhSO2, etc.; R4 = H, F, Cl, Br, iodo, OH, alkyl, alkoxy, fluoroalkoxy, cycloalkoxy, tetrahydrofurylalkoxy, tetrahydropyranalkoxy, etc.; A = CO, (substituted) C1-3 alkylene], were prepd. Thus, Me trans-1-(2-aminoethylamino)-4-[4-(3-chloro-2-fluorophenylamino)-7-methoxyquinazolin-6-yloxy]cyclohexanecarboxylate (prepn. given) was stirred with aq. NaOH in MeOH for 3 h to give 57% ant-9-4-(3-chloro-2-fluorophenylamino)-7-methoxyquinazolin-6-yloxy]-1,4-diazaspiro[5,5]undecan-5-one. It inhibited EGFR-dependent proliferation of murine hematopoietic cells with IC50 = 1-4 nM.
SciFinder records are indexed to ensure full retrieval of substances and concepts

### Concepts

- **Bronchitis**
  - allergic, treatment; prepn. of quinazolinyloxy spiroheterocycles as tyrosine kinase inhibitors
- **Bronchial disease**
  - Obstructive pulmonary disease
- **Bronchiectasis**
  - treatment; prepn. of quinazolinyloxy spiroheterocycles as tyrosine kinase inhibitors
- **Bronchitis**
  - Sinusitis
  - chronic, treatment; prepn. of quinazolinyloxy spiroheterocycles as tyrosine kinase inhibitors
- **Cholinergic antagonists**
  - H1-antihistamines
  - Dopamine agonists
  - β-Adrenoceptor agonists
  - coadministration; prepn. of quinazolinyloxy spiroheterocycles as tyrosine kinase inhibitors
- **Corticosteroids**
  - coadministration; prepn. of quinazolinyloxy spiroheterocycles as tyrosine kinase inhibitors
  - Therapeutic use; Biological study; Uses

### Substances

- **65154-06-5** Platelet activating factor
  - antagonists, coadministration; prepn. of quinazolinyloxy spiroheterocycles as tyrosine kinase inhibitors
  - Biological study, unclassified; Biological study
- **9036-21-9**
  - 73836-78-9 Ltd4
  - 115926-52-8 P13 kinase inhibitors
  - coadministration; prepn. of quinazolinyloxy spiroheterocycles as tyrosine kinase inhibitors
  - Biological study, unclassified; Biological study
- **79079-06-4** Egfr kinase
  - prepn. of quinazolinyloxy spiroheterocycles as tyrosine kinase inhibitors
  - Biological study, unclassified; Biological study
- **1178976-72-1P**
  - prepn. of quinazolinyloxy spiroheterocycles as tyrosine kinase inhibitors
  - Pharmacological activity; Reactant; Synthetic preparation; Therapeutic use; Biological study; Preparation; Uses; Reactant or reagent
Is this substance novel?

Depend on SciFinder to assess the uniqueness of your compound

- The most current and complete collection of disclosed chemical substances covering all areas of chemistry
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Source: WO2008110314
Specific compounds are often not completely identified in the original document.

Compound 34: Diisopropyl azodicarboxylate (DIAD) (1.20 mL, 6.08 mmol) was added to triphenylphosphine (1.60 g, 6.08 mmol) in THF (100 mL) at 0 °C, and was stirred for half an hour during which time the yellow solution became a paste.

Compound 14 (2.58 g, 4.06 mmol) and p-nitrobenzoic acid (0.81 g, 4.87 mmol) were dissolved in THF (50 mL) and added to the paste. The resulted mixture was stirred at ambient temperature overnight. Water (100 mL) was added and the mixture was made slightly basic by adding NaHCO₃ solution followed by extraction with EtOAc (3x50 mL). The combined extracts were washed with brine once and dried over anhydrous Na₂SO₄. The desired product (2.72 g, 87% yield) was isolated by SiO₂ chromatography (Et₂O/hexanes 1:1).

The compound has the following NMR data:
- \( \text{H} \_1: 8.30-8.26 (m, 2 \text{H}) \)
- \( \text{H} \_2: 8.21-8.16 (m, 2 \text{H}) \)
- \( \text{H} \_3: 4.02 (bs, 1 \text{H}) \)
- \( \text{H} \_4: 3.90 (bs, 1 \text{H}) \)
- \( \text{H} \_5: 2.29-2.19 (m, 1 \text{H}) \)
- \( \text{H} \_6: 2.07-1.06 (m, 1 \text{H}) \)
- \( \text{H} \_7: 1.69-1.34 (m, 3 \text{H}) \)
- \( \text{H} \_8: 0.70 (s, 3 \text{H}) \)

The compound also has the following mass spectra:
- \( m/e: ([M+Na]^{+}) 537 \)
- \( m/e: ([M+K]^{+}) 559 \)
- \( m/e: ([M+Na]^{+}) 537 \)
- \( m/e: ([M+K]^{+}) 559 \)

The isolated compound is a yellow solid. The CAS RN 20376-03-6 is highlighted.
SciFinder has unparalleled capabilities for exact, substructure, similarity, and Markush searching.
What is known about this substance?

If it’s important, SciFinder has it.
SciFinder offers a collection of properties that are valuable in every stage of discovery

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Biological</th>
<th>Structure-related</th>
<th>Spectra</th>
<th>Thermal</th>
</tr>
</thead>
</table>
| • Freely rotatable bonds  
• Hydrogen Donors and Receptors  
• Intrinsic Solubility (Mass and Molar)  
• Koc  
• logD  
• logP  
• Molecular Weight  
• pKa  
• Vapor Pressure  
• Dissociation Constant  
• Partition Coefficient | • Bioconcentration Factor  
• LC50  
• LD50  
• NOAEL/LoEL | • Particle Size  
• Polar Surface Area  
• X-Ray Diffraction Pattern | • Carbon-13 NMR  
• Proton NMR  
• IR Absorption  
• Mass Spectrum | • Boiling Point  
• Enthalpy  
• Entropy  
• Flash Point  
• Melting Point |
What is the best way to synthesize this substance?
View experimental procedures directly in SciFinder

**Overview**

<table>
<thead>
<tr>
<th>Steps/Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 R:4-DMAP, S:DMF, 18 h, rt</td>
</tr>
<tr>
<td>2.1 R:AcOK, C:95464-05-4, rt; 12 h, 80°C; 80°C → rt</td>
</tr>
<tr>
<td>3.1 R:HCl, S:Dioxane, S:CH₂Cl₂, 12 h, 40°C; 40°C → rt</td>
</tr>
<tr>
<td>3.2 R:NaHCO₃, S:H₂O, pH 8</td>
</tr>
<tr>
<td>4.1 R:Disodiumcarbonate, C:PdCl₂(PhH)₂, S:H₂O,</td>
</tr>
<tr>
<td>S:(CH₂OMe)₂, rt; 16 h, 87°C</td>
</tr>
<tr>
<td>5.1 R:HCl, S:MeOH, S:Dioxane, S:CH₂Cl₂, 1 h, rt</td>
</tr>
</tbody>
</table>

**Notes**

4) Suzuki coupling, Reactants: 4, Reagents: 5, Catalysts: 2, Solvents: 6, Steps: 5, Stages: 6, Most stages in any one step: 2

**References**

Combination of a c-Met antagonist and an aminoheteroaryl compound for the treatment of cancer

By Goetsch, Lilane
From PCT Int. Appl., 2010003992, 14 Jan 2010

**Experimental Procedure**

**Step 1**

General Procedure 62: To a solution of 5-bromo-3-[(R)-1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine (12.83 g, 33.76 mmol) in anhydrous DMF (100 mL) was added di- tert-butyl dicarbonate (21.25 g, 97.35 mmol) and 4-dimethylami[pi]pyridine (0.793 g, 6.49 mmol). The reaction was stirred at ambient temperature for 18 hours under nitrogen. To the mixture was added saturated NaHCO₃ solution (300 mL), and extracted with EtOAc (3×250 mL). The combined extracts were washed with water (5×100 mL), sat. NaHCO₃, and brine, then dried over Na₂SO₄. After filtration, evaporation, and high vacuum drying, di-boc protected 5-bromo-3-[(R)-1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine was obtained as an off-white foam solid (19.29 g, 100% yield). ¹H NMR (DMSO-d₆, 400 MHz) δ 8.18 (d, 1H), 7.83 (d, 1H), 7.59 (dd, 1H), 7.48 (t, 1H), 6.25 (q, 1H), 1.75 (d, 3H), 1.39 (s, 9H), 1.19 (s, 9H).

**Step 2**

To a solution of the di-boc protected 5-bromo-3-[(R)-1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine (19.58 g, 33.76 mmol) in DMSO (68 mL) was added potassium acetate (11.26 g, 114.78 mmol) and bis(pinacolato) diboron (10.29 g, 40.51 mmol). The mixture was degassed and
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W.M. Keck Professor of Chemistry
Scripps Research Institute

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