Privileged Scaffolds or Promiscuous Binders: A Glance of Pyrrolo [2,1-*f*][1,2,4]*triazines* and Related Bridgehead Nitrogen Heterocycles in Medicinal Chemistry

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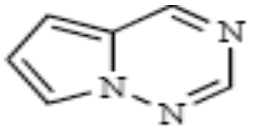
Outline

- Introduction
- Findings
    - Pharmacological Activities of Pyrrolo[2,1-F][1,2,4] Triazines
    - Pyrrolo[2,1-F][1,2,4]Triazine-related Bridgehead Nitrogen Heterocycles
- Summary and Perspective

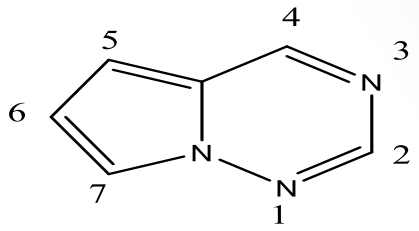
What is the purpose of identifying Pyrrolo[2,1-*f*][1,2,4]*triazine scaffold and its bridgehead nitrogen bioisosters?*



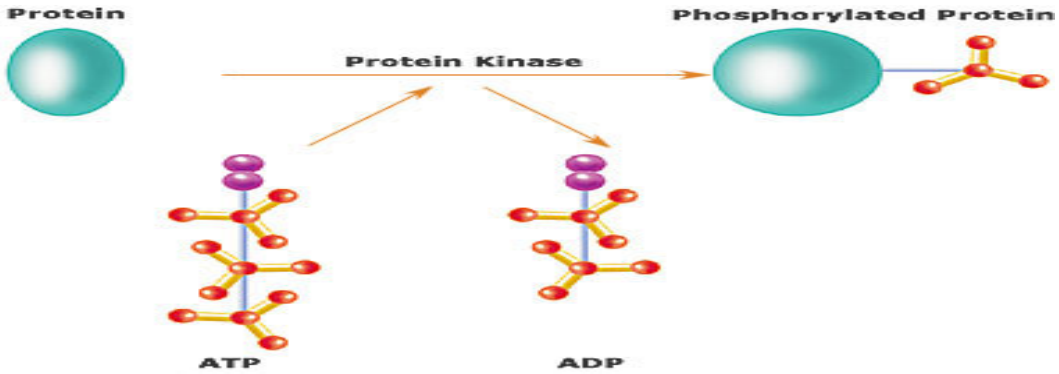
pyrrolo[1,2-*f*][1,2,4]triazine

To highlight the importance and the therapeutic potential of these scaffolds as heterocyclic privileged medicinal scaffolds.

Introduction



- Pyrrolo[2,1-f][1,2,4]triazine is a unique bridgehead nitrogen heterocycle that is considered as a privileged scaffold.
- pyrrolo[2,1-f][1,2,4]triazine have been identified as a versatile scaffold for the discovery of kinase inhibitors
- kinase is an enzyme that phosphorylates the substrates bound.
- Kinase enzymes inhibition therapy is becoming a very considerable field in drug discovery.



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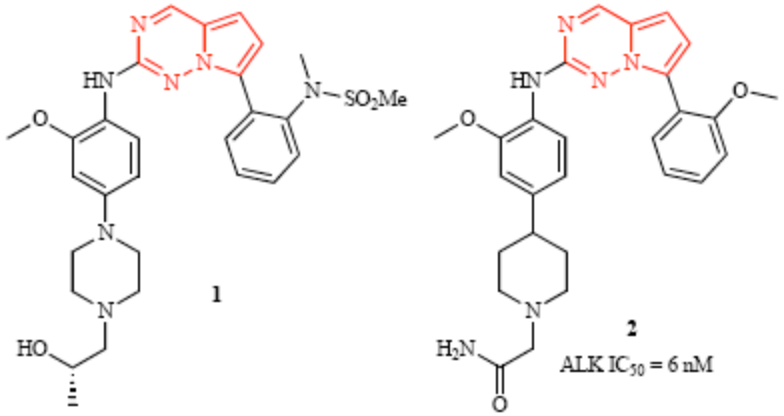
Anaplastic Lymphoma Kinase (ALK) Inhibitors

- Novel series of 2,7-disubstituted-pyrrolo[2,1-f][1,2,4]triazine derivatives has been developed as advanced ALK inhibitors
- Superior efficacy in depth *in vitro/in vivo* was displayed in the lead compound (compound 1).
- Piperidine-derived analogue (compound 2) demonstrated favorable anticancer efficacy, metabolic stability and oral bioavailability



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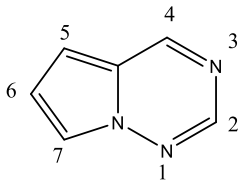
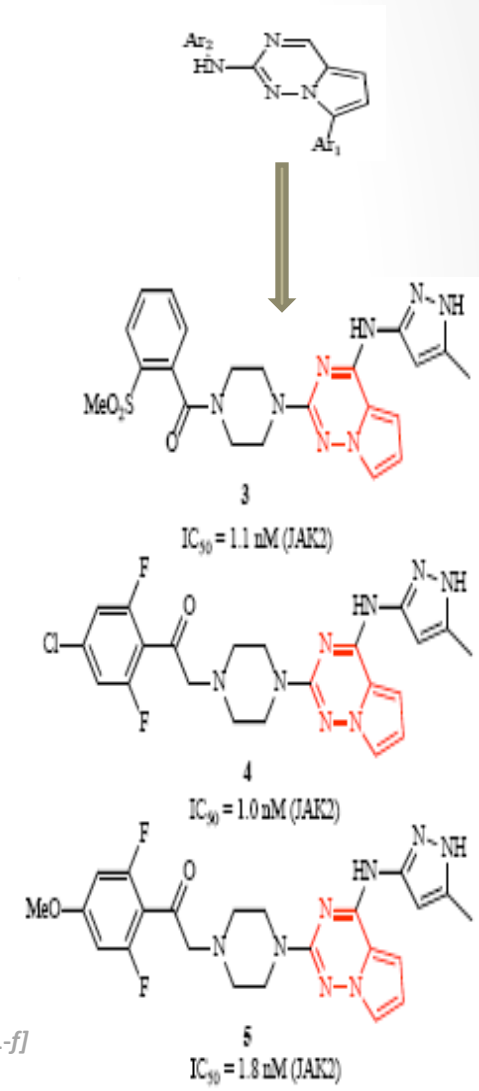
Janus Kinase 2 (JAK2) Inhibitor



- Other series of 2,7-pyrrolo[2,1-f][1,2,4]triazines was reported as potent JAK2 inhibitors.
- To minimize cytotoxicity and glutathione metabolite formation, aniline substituent at C2 was modified.
- SAR-based discovery of analogues (Compounds 3-5) with:
  - significantly improved bioactivity *in vitro* and cellular potency
  - JAK3 selectivity
  - poor metabolic stability



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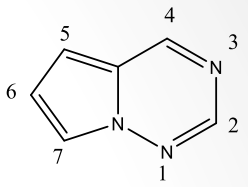
VEGFR-2, EGFR and/or HER2 Inhibitors

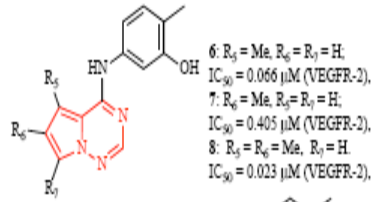


- Pyrrolo[2,1- f][1,2,4]triazine template was also identified as a novel VEGFR-2, EGFR and/or HER2 kinase inhibitor nucleus.

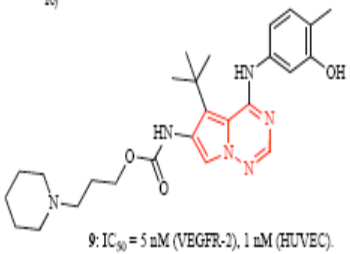
- SAR at the *C-5, C-6 and C-7 sites of the 4-(3-hydroxy-4-* methylphenylamino)pyrrolo[2,1-f][1,2,4]triazine scaffold led to compounds (Compounds 6-10) with robust *in vitro potency against:*
  - *VEGFR-2* and/or EGFR kinase
  - VEGF-dependent proliferation of human umbilical vein endothelial cells

- It was found that incorporation of a basic amino group on the C-6 side chain of the pyrrolotriazine core could reduce the glucuronidation of the phenol group

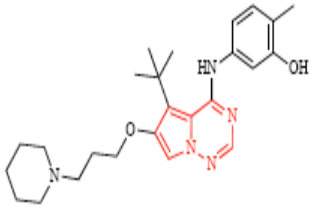
- Another *novel series of pyrrolo[2,1-* f][1,2,4] triazine-based dual HER2 and EGFR inhibitors was identified, having carbamates at C-6 (compounds 11-13)



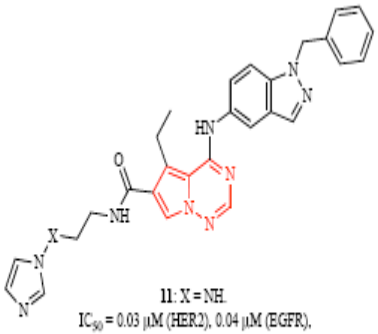
6: R_5 = Me, R_6 = R_7 = H;
IC_{50} = 0.066 μM (VEGFR-2), 0.346 μM (EGFR).
7: R_6 = Me, R_5 = R_7 = H;
IC_{50} = 0.405 μM (VEGFR-2), 0.654 μM (EGFR).
8: R_5 = R_6 = Me, R_7 = H.
IC_{50} = 0.023 μM (VEGFR-2), 0.200 μM (EGFR).



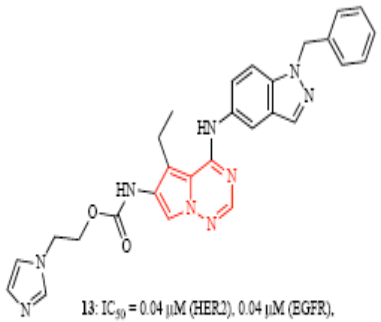
9: IC_{50} = 5 nM (VEGFR-2), 1 nM (HUVEC).



10: IC_{50} = 4 nM (VEGFR-2), 1 nM (HUVEC).



11: X = NH.
IC_{50} = 0.03 μM (HER2), 0.04 μM (EGFR), 7.0 μM (BT472), 5.8 μM (Sal2).
12: X = O.
IC_{50} = 0.24 μM (HER2), 0.17 μM (EGFR), 3.1 μM (BT472), 1.6 μM (Sal2).



13: IC_{50} = 0.04 μM (HER2), 0.04 μM (EGFR), 0.86 μM (BT472), 0.46 μM (Sal2).

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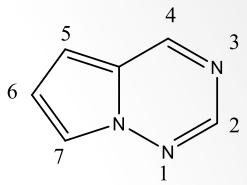
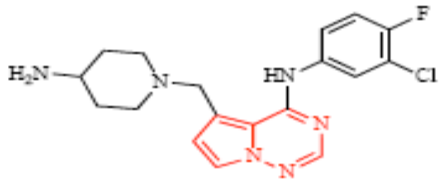
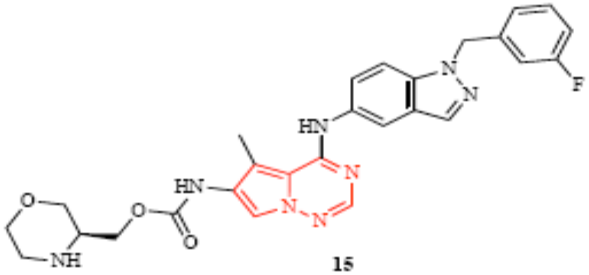
VEGFR-2, EGFR and/or HER2 Inhibitors





14

IC_{50} = 0.01 μM (HER2), 0.006 μM (EGFR), 0.12 μM (N87).



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- Compound 14 exhibited excellent oral efficacy in both HER2 and EGFR-driven human tumor xenograft models.

- *BMS*- 599626 (compound 15) is drug candidate for the therapy of solid tumors, showing:
  - promising biochemical potency
  - HER1/ HER2 kinase selectivity
  - favorable pharmacokinetic profiles and good *in vivo activity*

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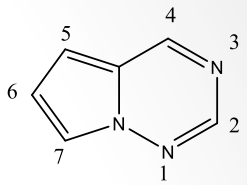
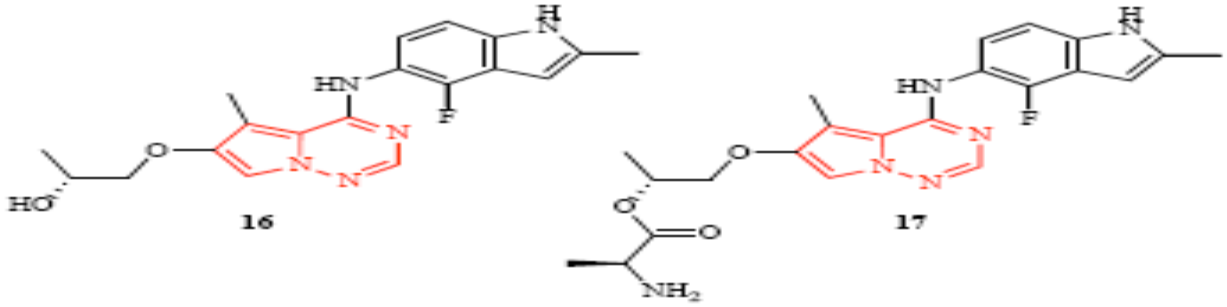
VEGFR-2, EGFR and/or HER2 Inhibitors





- SAR investigations demonstrated that a substituted alkoxy group at the 6-position and a methyl group at the 5-position of the pyrrolo[2,1-f] [1,2,4]triazine nucleus gave potent inhibitors.

- BMS-540215 (compound 16) showed:
  - Optimized of biochemical potency, kinase selectivity, and pharmacokinetics
  - *in vitro toxic* effects

- BMS 582664 (compound 17), the L-alanine prodrug of compound 16, is currently under evaluation in phase II clinical trials for the treatment of solid tumors.

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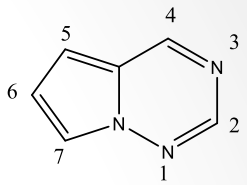
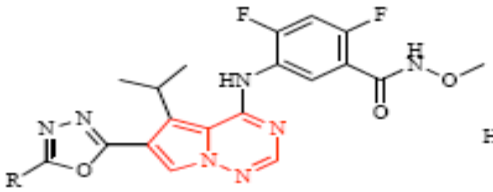
VEGFR-2, EGFR and/or HER2 Inhibitors





18: R = CHF_2

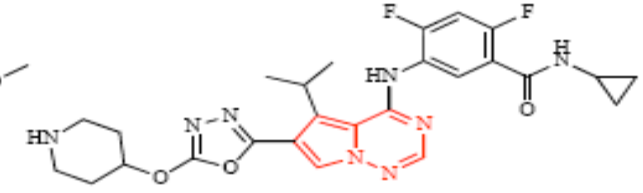
IC_{50} = 57 nM (VEGFR-2), 100 nM (FGFR1), 17 nM (VEGF/HUVECs), 21 nM (FGF/HUVECs).

19: R = $CH_2SO_2CH_3$

IC_{50} = 16 nM (VEGFR-2), 16 nM (FGFR1), 2.1 nM (VEGF/HUVECs), 4.6 nM (FGF/HUVECs).

20: R = $CF_2SO_2CH_3$

IC_{50} = 53 nM (VEGFR-2), 220 nM (FGFR1), 27 nM (VEGF/HUVECs), 130 nM (FGF/HUVECs).



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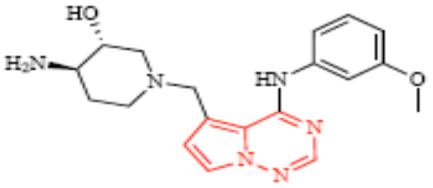
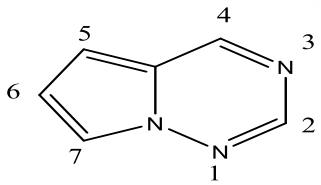
IC_{50} = 11 nM (VEGFR-2), 5000 nM (CYP3A4), 23 nM (HUVEC).



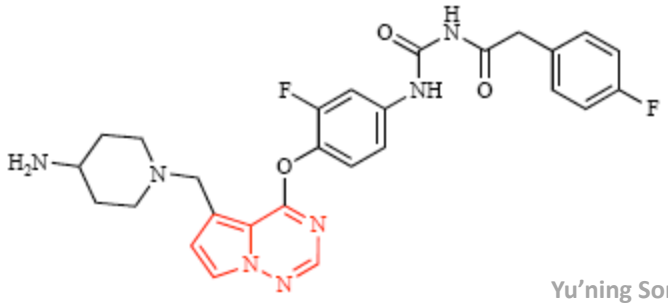
BMS-690514 (22)

- Substituting 2,4-difluoro-5-(methoxycarbamoyl)phenylamino and the 2,4-difluoro-5-(cyclopropylcarbamoyl)phenylamino group at the C-4 site led to potent and selective tyrosine kinase inhibitors activity
- Substituting heterocyclic bioisosteres at C-6 provided compounds with outstanding oral bioavailability in mice.
- Antitumor efficacy was observed with compounds 18-21 against established L2987 human lung carcinoma xenografts implanted in athymic mice.
- BMS-690514 (22) was identified as a potent and selective inhibitor of the tyrosine kinase activity of EGFR/pan-HER.

Met Kinase



- Identification of pyrrolo[2,1-f][1,2,4]triazine-based inhibitors of Met kinase activity from an initial library screening.
- Polar moieties at C-5 of the pyrrolotriazine scaffold showed tremendous improvements in *in vitro potency.*
- malonamide and acylurea substituents were used as substituents to get with increased potency in GTL-16 human gastric carcinoma cell line.



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IC_{50} = 0.045 μM (Met)

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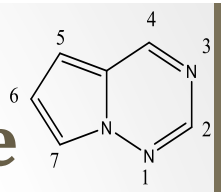
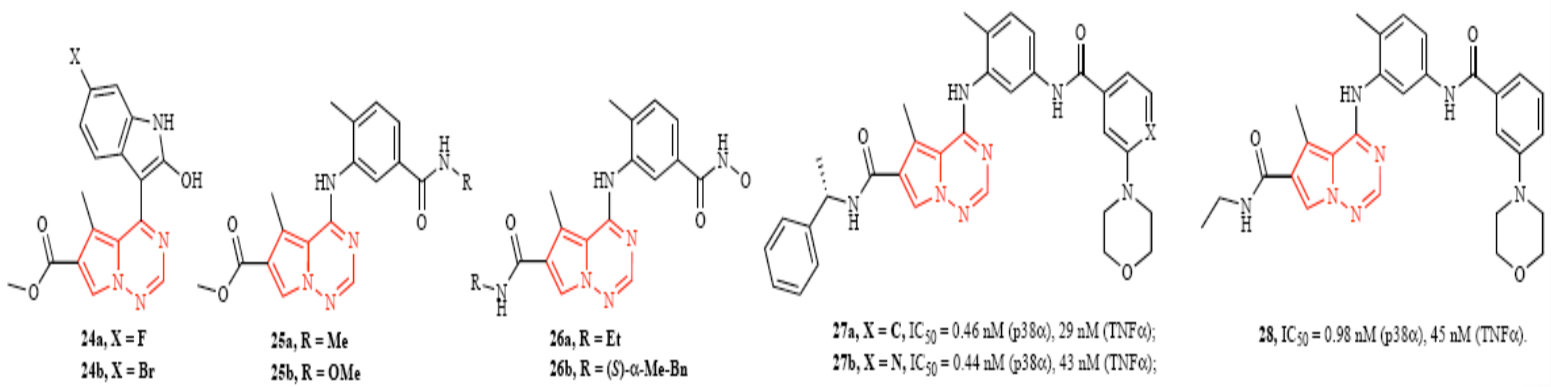
p38α Mitogen-activated Protein (MAP) Kinase Inhibitor





24a, X = F
24b, X = Br

25a, R = Me
25b, R = OMe

26a, R = Et
26b, R = (*S*)-α-Me-Bn

27a, X = C, IC_{50} = 0.46 nM (p38α), 29 nM (TNFα);
27b, X = N, IC_{50} = 0.44 nM (p38α), 43 nM (TNFα);

28, IC_{50} = 0.98 nM (p38α), 45 nM (TNFα).

- Compound 24a was discovered as a novel inhibitor of p38 mitogen-activated protein (MAP) kinase.
- Compound 25b showed excellent p38 kinase inhibition.
- Compounds 26a and 26b were given to animal models to show significant inhibition of disease progression
- Compounds 27 and 28 showed distinguished inhibition of LPS-stimulated TNF-α production.

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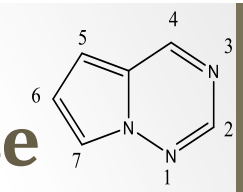
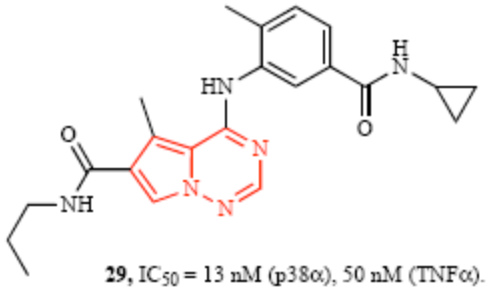
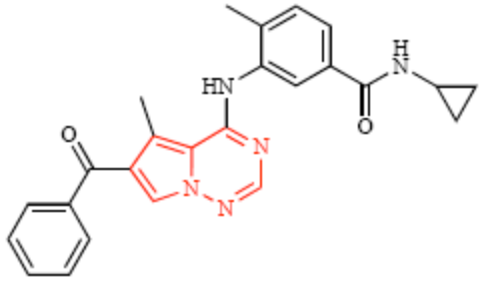
p38α Mitogen-activated Protein (MAP) Kinase Inhibitor





29, IC_{50} = 13 nM (p38α), 50 nM (TNFα).



30, IC_{50} = 4 nM (p38α), < 8.2 nM (PBMC).

- Compound 29 (BMS-582949) is a highly selective p38α MAP kinase inhibitor
- Other highly potent and orally bioavailable inhibitors such as compound 30 were discovered by incorporating aryl and heteroaryl groups at C-6.

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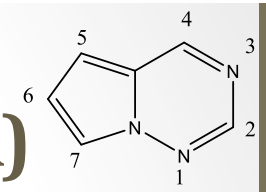
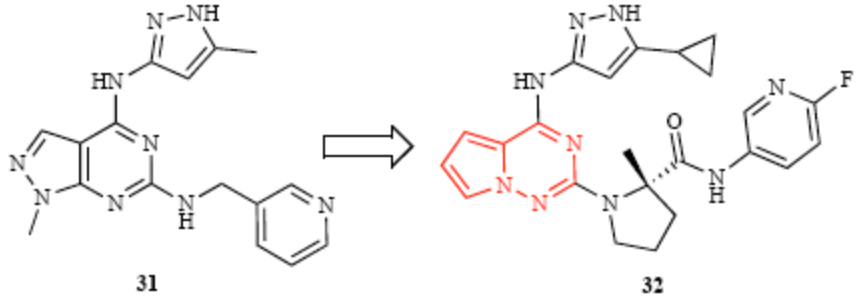
Insulin-like Growth Factor Receptor (IGF-1R) Kinase Inhibitor





31 32

- The pyrazolo[3,4-d]pyrimidine,(compound 31) was used as a lead to search for the novel insulin-like growth factor receptor (IGF-1R) kinase inhibitor with good potency.

- 2,4-disubstituted pyrrolo[1,2-f][1,2,4] triazine (compound 32, BMS-754807) showed:
  - Efficacy
  - Oral activity

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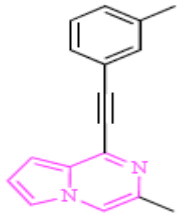
PYRROLO[2,1-F][1,2,4]TRIAZINE-RELATED BRIDGEHEAD NITROGEN HETEROCYCLES

- **Pyrrolo[1,2-a]pyrazine**
  - Potent and selective non-competitive mGluR5 (Metabotropic glutamate receptor 5) antagonists. (Compound 33)



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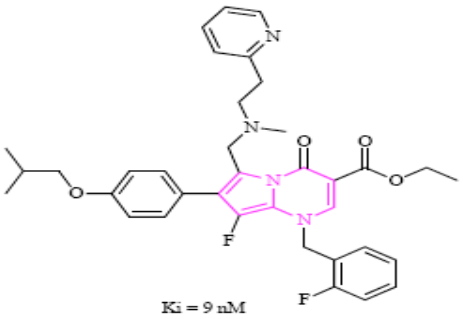
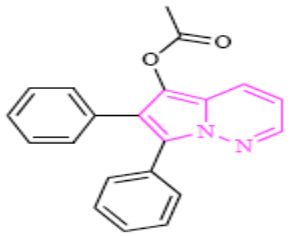
- **Pyrrolo[1,2-a]pyrimidine**
  - Small molecule GnRH antagonists. (Compound 38)



Ki = 9 nM

38

- **Pyrrolo[1,2-b]pyridazine**
  - various biological applications
  - antioxidant properties (Compound 39)



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- **Pyrazolo[1,5-a]pyrimidine**
- Different pharmacological activities:
  - Serotonin 5-HT(6) receptor antagonists (Compound 42)
  - Diacylglycerol acyltransferase 1 inhibitor
  - Xanthine oxidase inhibitors

42

K_i = 0.088 nM

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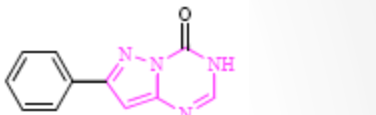
PYRROLO[2,1-F][1,2,4]TRIAZINE-RELATED BRIDGEHEAD NITROGEN HETEROCYCLES

- **Pyrazolo[1,5-a][1,3,5]Triazine**
  - Diversity of pharmacological activities, such as xanthine oxidase inhibitor(compound 57), protein kinase CK2 inhibitor, and LPS-induced TNFα release inhibitors

- **Imidazo[1,2-a]pyrazine**
  - Diversity of pharmacological activities, eg. Phosphoinositide-3-kinase (PI3K) inhibitor. (Compound 69)

- **Imidazo[1,5-a]pyrazine**
  - IGF-1R inhibitor OSI-906 (77)

- **Imidazo[1,2-a]pyridine**
  - 5-lipoxygenase (5-LO) inhibitor 80



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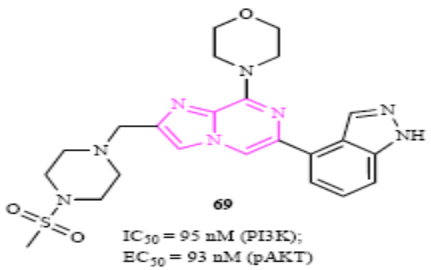
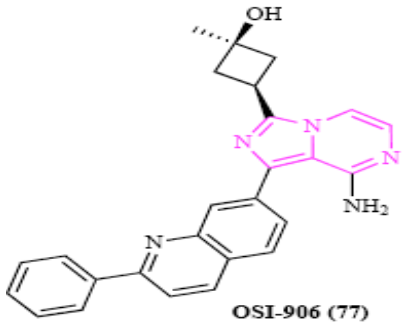


69

IC_{50} = 95 nM (PI3K);
EC_{50} = 93 nM (pAKT)



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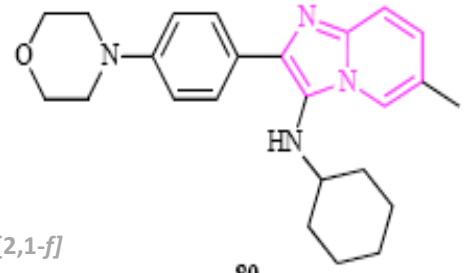

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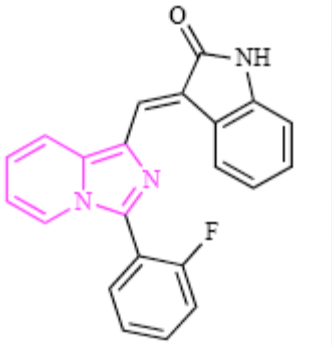
PYRROLO[2,1-F][1,2,4]TRIAZINE-RELATED BRIDGEHEAD NITROGEN HETEROCYCLES

- **Imidazo[1,5-a]pyridine**
  - Anticancer activity (Compound 101)
  - Positive allosteric modulators of the metabotropic glutamate 2 (mGlu2) receptor

- **Imidazo[1,2-a]pyrimidine**
  - wide spectrum of biological activities, such as cytomegalovirus and/or varicella-zoster virus inhibitor (compound 104) and androgen receptor antagonist

- **Imidazo[5,1-f][1,2,4]triazine and imidazo[1,5-a][1,3,5] triazine**
  - A broad spectrum of pharmacological activities. Eg. influenza A virus inhibitor (Compound 123)

- **[1,2,4]Triazolo[1,5-a]pyridine**
  - AKT allosteric inhibitor (Compound 129)
  - DNA gyrase (GyrB)/topoisomerase IV (ParE) inhibitor
  - Antifungal agents
  - Non-steroidal pregnancyterminating agents



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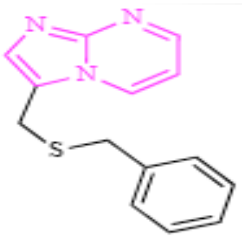
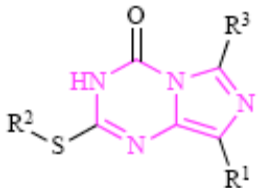
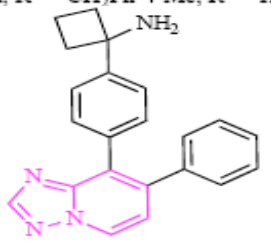


104



123 $R^1 = (CH_2)_5OCH_2Ph$, $R^2 = CH_2Ph\text{-}4\text{-}Me$, $R^3 = H$



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Summary and Perspective

- Pyrrolo[2,1-f][1,2,4]triazine heterocycle will certainly remain a privileged scaffold and versatile building block in drug discovery.

- Bioisosteric bridgehead nitrogen heterocycles have a diverse non-selective pharmacological activities.

- The rapid expanding diversity of substituents around bridgehead nitrogen heterocycle core, provided opportunities for further investigation of their action mechanism, specificity and selectivity.

Thank You