Recent Advancements in Small Molecule Inhibitors of Insulin–like Growth Factor-1 Receptor (IGF-1R) Tyrosine Kinase as Anticancer agents

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Abstract: Advancements in understanding of the genetics, genomics, biochemistry and the pharmacology of cancer in human, have driven the current cancer chemotherapy to intently focus on development of target-based approaches rather than conventional approaches. From among the various targets identified, validated and inhibited at different hallmarks of cancer, protein tyrosine kinases (PTKs) have been exploited the most. Insulin receptors (IRs), insulin like growth factor receptors (IGF-1R) and their hybrid receptors belong to tyrosine kinase receptor (TKR) family, constitute a structural homology among them and generate a growth promoting IGF system on binding with either insulin, IGF-1 or IGF-2. The system induces the mitogenic effects through a torrent of cell signals produced as a result of cross talk with other growth promoting peptides and steroidal hormones, ultimately resulting in hijacking apoptosis and increasing cell proliferation and cell survival in cancer cells. Various strategies such as anti-IGF-1R antibodies, IGF-1 mimetic peptides, antisense strategies, IGF-1R specific peptide aptamers, targeted degradation of IGF-1R and expression of dominant negative IGF-1R mutants have been explored to inhibit the IGF-1R signaling. However, targeting IGF-1R with small molecules has gained considerable attention in last few years due to their ease of synthesis, ease of optimization of absorption, distribution, metabolism, excretion and toxicity (ADMET) parameters, oral route of administration, lesser side effects and cost effectiveness. The present review provides a broad overview and discusses the highlights on discoveries, SAR studies and binding interactions of small molecules with either IGF-1R active or allosteric sites reported till date.

Keywords: Cancer, IGF-1R, IGF-1R inhibitors, IR, SAR, Tyrosine Kinases.

1. INTRODUCTION

Human genome sequence analysis identified about 518 human protein kinases (constituting approximately 1.7% of all the human genes), out of which at least 90 tyrosine kinases (TKs) have been marked where 58 are receptor tyrosine kinases and 32 are non receptor tyrosine kinases [1-3]. TKs being characterized by their ability to catalyze the phosphorylation of tyrosine amino acid residue in the protein, are involved in the wide range of cellular signaling pathways and events-proliferation, metabolism, differentiation and apoptosis under normal cell conditions as well as in various disease states [4,5]. Imatinib which targets the bcr-abl tyrosine kinase had a high therapeutic index against chronic myelogenous leukaemia (CML) and became the prototype of successful tyrosine kinase inhibitors (TKIs) that have had FDA approval [6]. The success of imatinib against CML has prompted researchers to develop new TKIs for the management of other types of cancer including renal cell carcinoma [7], non-small-cell lung cancer [8], colon cancer [5,9] and many more [10-12]. Moreover, the potential of TKIs for the treatment of other diseases such as cardiac hypertrophy, pulmonary hypertension, lung fibrosis, rheumatoid disorders, atherosclerosis, in-stent restenosis and glomerulonephritis has also been extensively reviewed [5].

Insulin like growth factor (IGF) system is composed of tyrosine kinases [13]- insulin receptors (IRs) and insulin like growth factor–I receptor (IGF-1R) and non tyrosine kinase-insulin like growth factor–2 receptor (IGF-2R); and their ligands i.e. insulin, IGF-I and IGF-2; and six IGF-binding proteins (IGFBPs). The system plays a dominant role in maintaining the development and metabolic homeostasis but any disruption causes pathological conditions such as diabetes and cancers [14-24]. Both IR and IGF-1R are tetrameric glycoproteins ($\alpha_2\beta_2$) i.e. 2-α and 2- β subunits linked by disulfide bonds. Each α-subunit i.e. ~130 kDa, contains ligand binding site on the cysteine-rich region in the extracellular α-subunit, whereas each β-subunit contains the tyrosine kinase domain of ~90-95kDa [25-27, 30,31]. IGF-1R is quite homologous to IR, ranges from 45-65% in the ligand binding domain to 60-85% in the kinase and substrate recruitment domains (ATP binding region), which were accessed by alanine scanning mutagenesis of insulin [32] and alanine scanning mutagenesis of IGF-1R [32-37]. The main difference between IGF-1R and IR occurs in their enzymatic domain whereas a subtle difference has been observed in the hinge region (Thr 1053/Arg 1054 in IGF-1R Vs Ala1080/ His1081 in IR) [38]. In addition the C-terminal of the intracellular β-subunits of IR is structurally and functionally

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different from IGF-1R, in tyrosine units as there are three in IGF-1R and only two in IR [26,39]. Further, the unactivated, nonphosphorylated and fully activated, triply phosphorylated IGF-1R and IR differ structurally especially regarding the positions of the activation loop and αC helix [40,41].

In spite of high homology between IR and IGF-1R, both receptors maintain a separate and distinct functions as IR exhibits its dominant role in metabolic homeostasis (preferably in glucose metabolism) [42,43] while IGF-1R dominates in the cell development and proliferation processes [17,44]. However, in certain cases especially cancer and diabetes [45], IR in hybridization with IGF-1R [46], stimulates cell proliferation and differentiation [47-50]. Involvement and overexpression of IGF-1R in various types of malignancies [51] which include lung [52-53], breast [54-62], prostate [63-68], neuroendocrine [69], head and neck cancer [70], GIT cancers [71,72] for e.g, colorectal [73-78], hepatocellular [79-84] and pancreatic carcinomas [15,16,85-87] at preclinical [88] and clinical level [89,90] have been observed.

In signaling cascade of IGF-1R (Fig. **1**) [91], the ligands (IGF-1, Insulin, IGF-2) of receptors (IGF-1R, IR or their hybrid receptors) bind to extracellular α-subunit of the receptor, trigger the autophosphorylation of the tyrosine residues (Tyr1131, Tyr1135, Tyr1136 of the tyrosine kinase domain) [92] of intracellular β-subunit subsequently also allowing the trans-phosphorylation of opposite intracellular β-subunits [31]. After phosphorylation of the above key triplet tyrosine residues, other tyrosine residues of the juxtamembrane region especially tyrosine residue (Tyr950), kinase domain, and the –COOH terminus are also autophosphorylated. These phosphotyrosines exist in specific motifs such as Tyr-Xaa-Xaa-Met, which in turn, become the docking sites to recruit and phosphorylate the Src homology 2 domain-containing (SHC) adaptor proteins such as Grb-2 and phosphatidyl-inositol-3’-kinase (PI 3-Kinase) [93], which exist as a complex of two subunits p85(SH2-containing regulatory subunit) and p110 (the catalytic subunit), initiating a PI 3-Kinase pathway. Grb-2 (an SH-2 containing substrate) binds mSOS, a protein which exchanges GTP for GDP on Ras [94] results in the activation of Ras/Raf/mitogen-activated protein (MAP) kinase pathways [95-98]. A conformation change in RAS due to GTP binding induces phosphorylation and activation of RAF [99, 100]. Activated RAF further phosphorylates the MEK, which afterwards activates ERK-1 and ERK-2 via phosphorylation of their serine / theorine kinases of –Thr-Glu-Tyr- motif in the activation loop [100-103]. Activation of these, causes phosphorylation of cytoplasmic subtrates and nuclear translocation and activates various transcription factors (c-Myc [104-107], Ets factors [108-110], CREB [111-113], AP1 [114-116, 119] that regulate the expression of many genes [120-123]. Cytoplasmic substrate of ERK like procaspase-9, proapoptotic caspase-9 protein [124-128] gets phosphorylated at Thr125 residue itself by ERK, provides the steric hindrance in conformational change of the proenzyme to active caspase-9, thus enhances cell survival [129]. The pathway holds the regulation key of cell cycle progression and apoptosis or cell survival [130]. The activation of RAS/Raf/MEK/ERK pathway acts as development and progression of cancer as mutation occurs either in Ras or Raf in case of malignancies [131].

IGF-1R is also involved in a different downstream signaling PI3K/AKT pathway [132,133]. Harboring of IRS-1 either to phosphorylated tyrosine residue of juxtamembrane region or key triplet tyrosine residues of the IGF-1R hires regulatory subunit (p85) of PI3K [134-136], which in turn activates its catalytic subunit (p110) [137,138]. Phosphorylated PI3K activates membrane associated phosphatidylinositol 4,5-biphosphate (PIP_2), by phosphorylating it into phosphatidylinositol 3,4,5-biphosphate(PIP_3), resulting in membrane localization of phophatidylinsoitol-dependent kinase (PDK-1) [135,139,140]. This conversion of PIP_2 to PIP_3, recruits AKT to the membrane and leads to its phosphorylation [141,142]. The serine/threonine kinase of AKT phosphorylates different targets, which contribute in proliferation and antiapoptotic processes of the cell [143]. Like proapoptotic protein BAD, which normally induces apoptosis via the formation of heterodimers of antiapoptotic proteins BCL2 and BCL-XL whereas its phosphorylation at Ser112 and Ser136 by AKT [144,145] causes its own sequestration by binding to 14-3-3 proteins [146-148]. Activated AKT also does the phosphorylation and thus inactivation of GSK (Gycogen synthase kinase)-3β which induces glycogen synthesis [149,150]. Activated AKT may also phosphorylate serine/theorine kinase domain of mTOR via consequent inactivation of GTPase-activating heterodimeric protein tuberous sclerosis complex1/2 (TSC1/2) [151-153]. The inactivation of TSC1/2 relieves RHEB and activation of mTOR [154]. Researchers have exploited various downstream intracellular signaling proteins as anticancer drug targets involved in the pathways mentioned in the (Fig. **1**). Recently the role of IGF-1R in metastasis was disclosed as under experimental conditions targeting IGF-1R increases miRNA-7 level in gastric cancer which disrupts the EMT process, a prerequisite in metastasis [91,155]. In addition to these, other MicroRNA’s anticancer characteristics were also reported, MiR-139 inhibits the invasion and metastasis by targeting the IGF-1R axis in colorectal cancer [156] and MicroRNA-497 targets IGF-1R in suppressor of colorectal cancer [157].

2. SMALL MOLECULES AS INHIBITORS OF INSULIN LIKE GROWTH FACTOR RECEPTOR-1 (IGF-1R)

Several strategies [158,159] such as anti-IGF-1R antibodies [160-163], IGF-1 mimetic peptides [164,165], antisense strategies [166-169], IGF-1R specific peptide aptamers [46,170,171], targeted degradation of IGF-1R [158] and expression of dominant negative IGF-1R mutants [172-174] have been explored to inhibit the IGF-1R signaling at different hallmarks of cancer [60,158,175-179]. However, targeting IGF-1R with small molecules [180] has gained considerable attention in last few years due to their ease of synthesis and ease of optimization of absorption, distribution, metabolism, excretion and toxicity (ADMET) parameters, oral route of administration, lesser side effects and cost effectiveness. A review by Li *et al.* [181] had covered the literature on compilation of small molecules as IGF-1R inhibitors till the year 2009. During the preparation of the present review, a collection on several classes of synthetically and naturally occurring IGF-1R inhibitors in

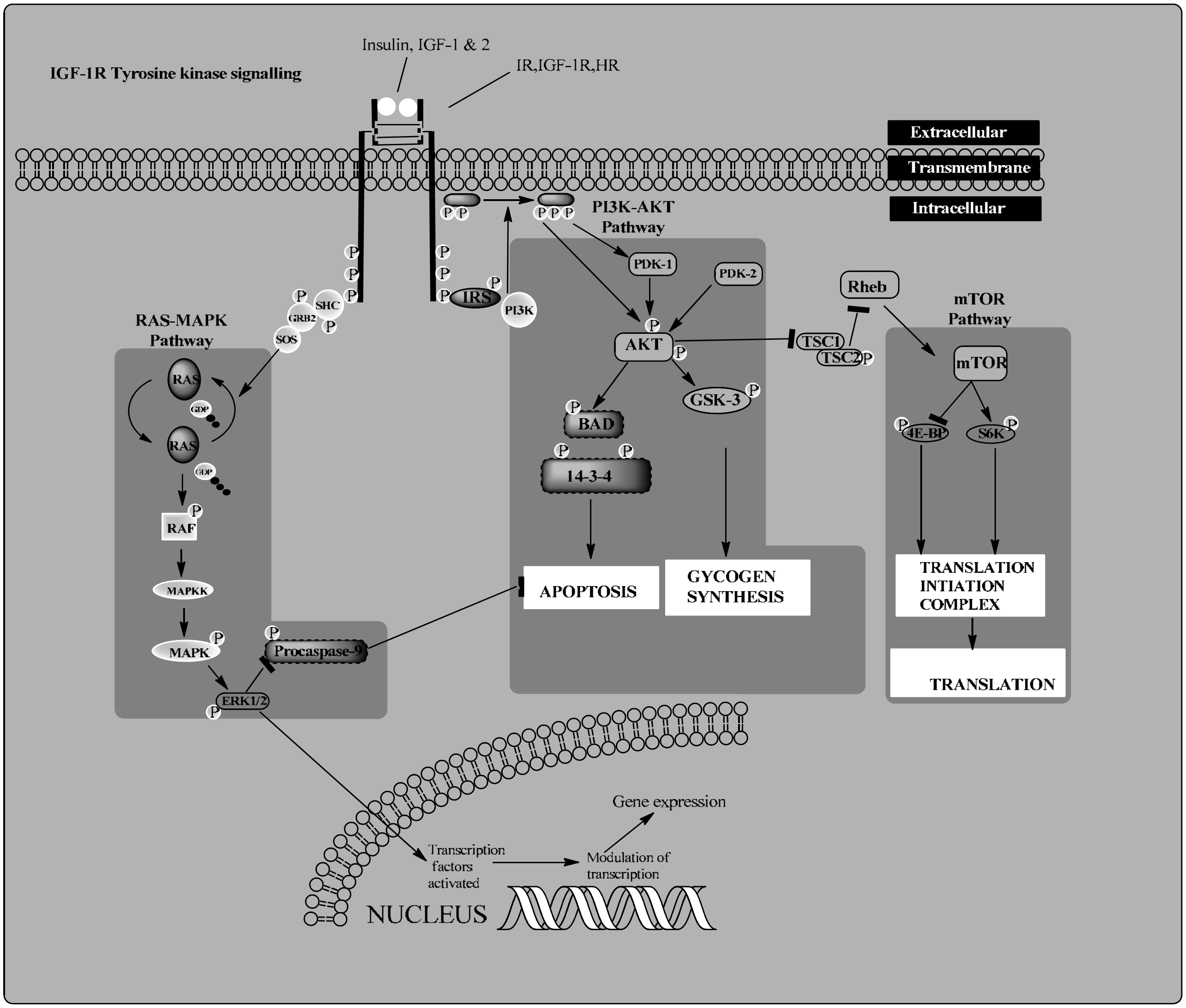
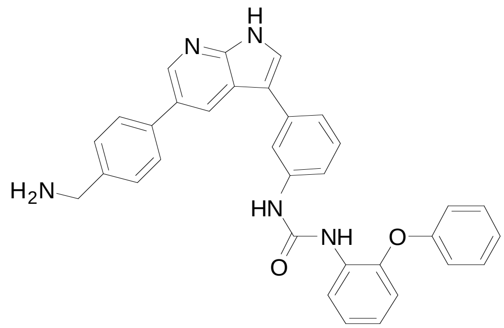
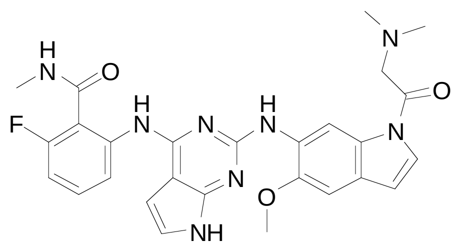
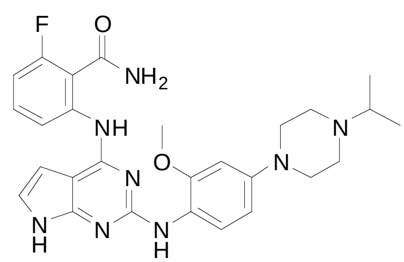
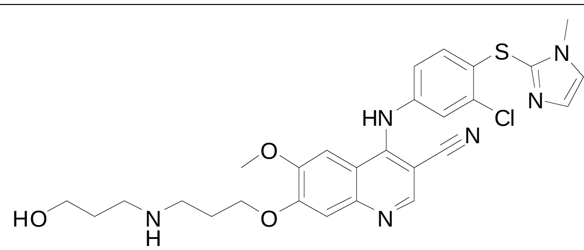
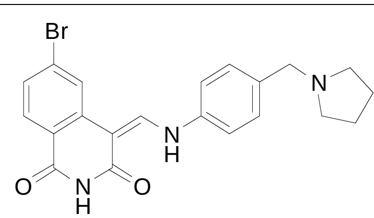
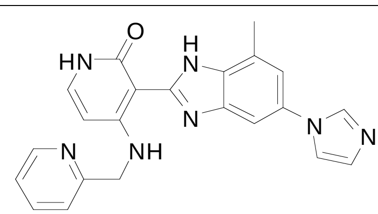


Fig. (1). Insulin and Insulin like growth factor mediated cell signaling cascade: Binding of Insulin and/or IGF-1/2 to IGF-1R, Insulin receptor(IR), hybrid receptor (HR) leads to the cell signaling as depicted above. SHC (Src homology 2 domain-containing), GRB2 (growth factor recptor-bound protein-2), SOS (son of sevenless, a guanine nucleotide exchange factor), MAPKK (mitogen-activated protein kinase), MAPK (mitogen-activated protein kinase), ERK-1/2 (extracellular signal regulated kinase), IRS(insulin receprtor substrate), PI3K (phosphatidyl-inositol-3’-kinase), PDK1/2 (phosphatidyl-inositol dependent kinase-1/2), AKT (AKR mouse thymoma kinase), GSK-3β (glycogen synthetase kinase-3β), TSC1/2 (tuberous sclerosis complex-1/2, a GTPase-activating hetrodimeric protein, called as hamartin/tuberin respectively), Rheb (ras homolog enriched in brain), mTOR, 4E-BP (elF-4E-binidng proteins) and S6K (ribosomal S6 family of kinases).

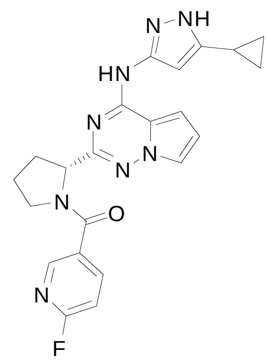
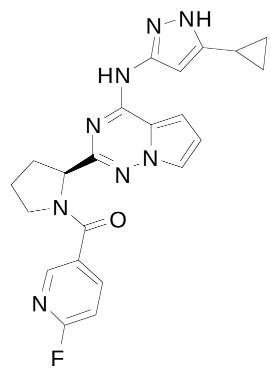
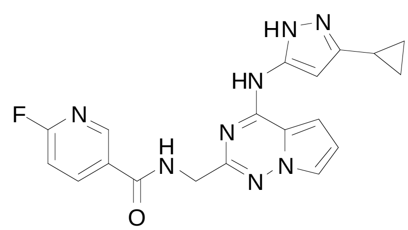
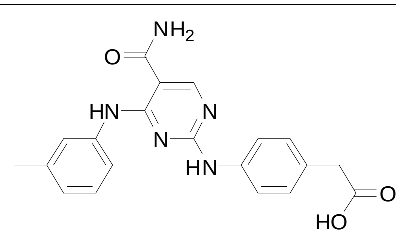
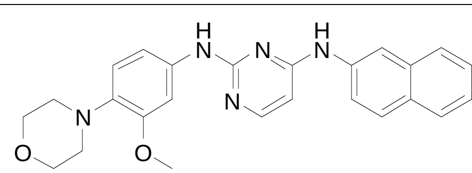
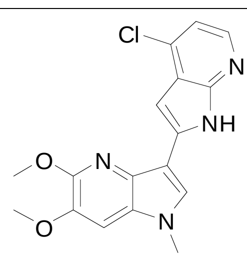
various stages of preclinical or clinical [182-184] attempted by Xue *et al*. [185]; appeared. The present review however, provides a broad overview and discusses the highlights on discoveries, SAR studies and binding interactions of small molecules of diverse chemotypes binding to IGF-1R active or allosteric sites reported till date.

The X-ray co-crystal structures of IGF-1R in complex with ANP (Adenosine 5′-(β,γ-imido)triphosphate; PDB code:1jqh; a synthetic analogue of ATP) [186] or with other compounds (Table **1**) reveal that hinge amino acids residues Glu 1080 and Met 1082 are conserved that participate in hydrogen bond acceptor/donor/acceptor triad either with adeninine or other heterocyclic systems such as imidazopyrazine, imidazotriazine, pyrrolopyrimidine, pyrimidine/triazine-quinolines/naphthalene, isoquinoline dione, hydantoin-quinoline, cyanoquinolines, benzimidazole-pyridone, thiazolidinediones etc. as shown in Fig. (**2**). The above mentioned classes of compounds also experience binding to other regions i. e. sugar, phosphate and hydrophobic regions of ATP binding site. The above reported crystal structures are being exploited for the structure based drug design and discovery of more potent and selective IGF-1R inhibitors.

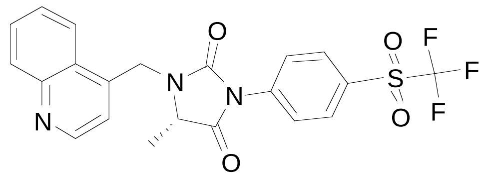
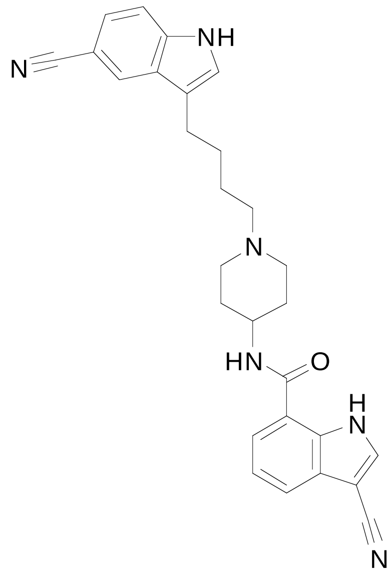
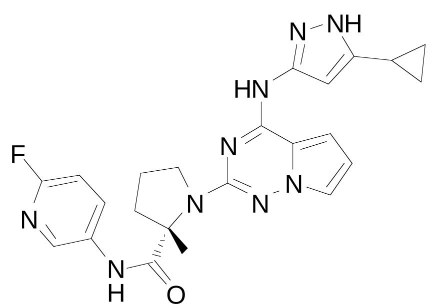
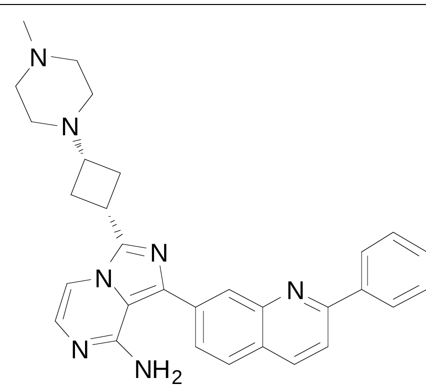
Table 1. Some Reported X-ray Co-crystal Structures of IGF-1R with the Inhibitor.

PDB Entry	IR/IGF-1R	Inhibitor	Resolution (Å)	Ref.
3ETA	IR Kinase domain		2.60	[187]
3EKK	IR kinase domain		2.10	[188,189]
3EKN	IR kinase domain		2.20	[188,189]
3F5P	IGF-1R		2.90	[190]
2ZM3	IGF-1R		2.50	[191]
2OJ9	IGF-1R		2.00	[192]

(Table 1) contd….

PDB Entry	IR/IGF-1R	Inhibitor	Resolution (Å)	Ref.
3NW5	IGF-1R		2.14	[193]
3NW6	IGF-1R		2.20	[193]
3NW7	IGF-1R		2.11	[193]
2Z8C	IR		3.25	[194]
3QQU	IGF-1R		2.90	[195]
3LVP	IGF-1R		3.00	[196]

(Table 1) contd….

PDB Entry	IR/IGF-1R	Inhibitor	Resolution (Å)	Ref.
3O23	IGF-1R		2.10	[197]
3LW0	IGF-1R		1.79	[198]
3I81	IGF-1R		2.08	[199]
3D94	IGF-1R		2.30	[200]

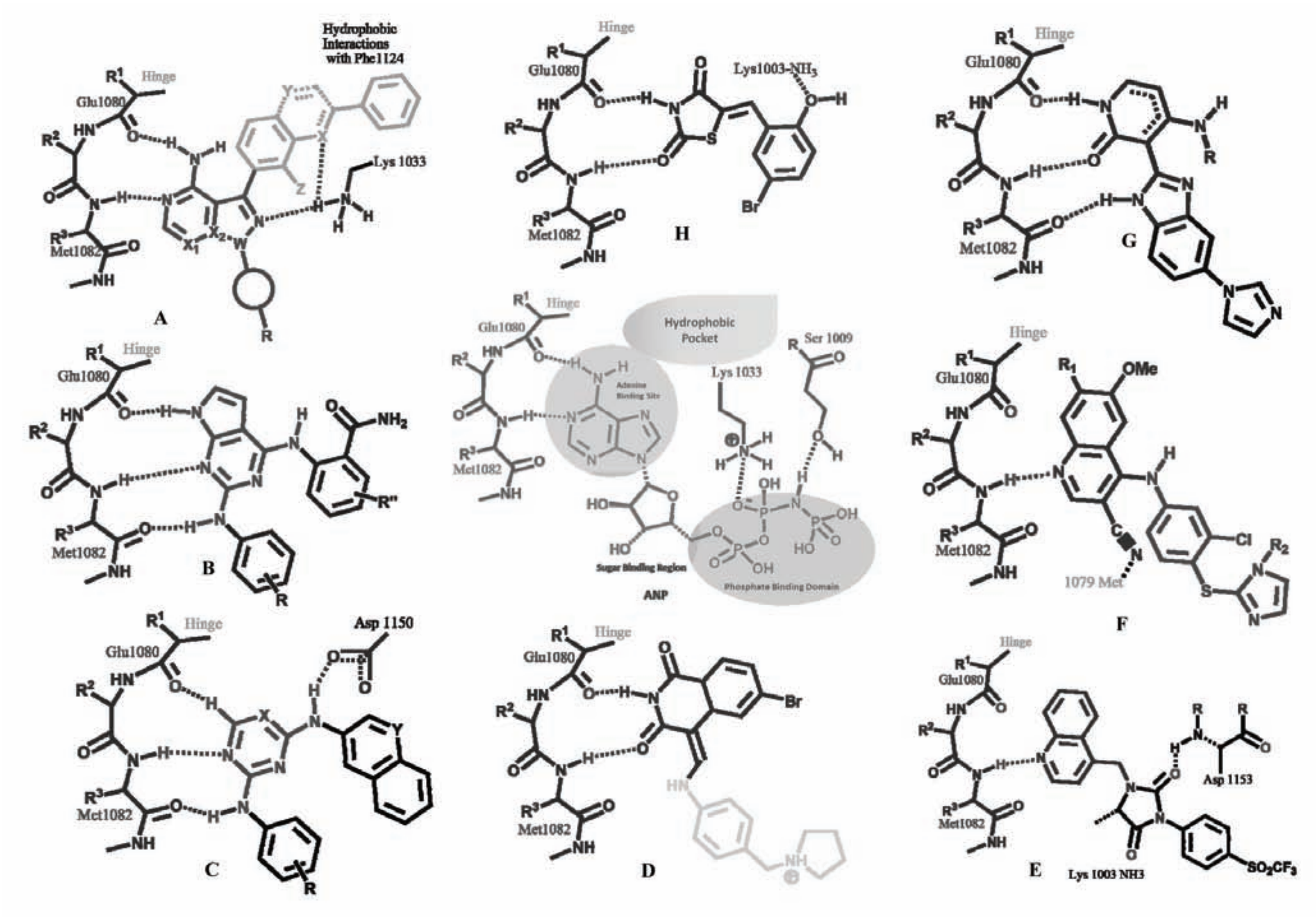


Fig. (2). Major classes of ATP-competitive inhibitors of IGF-1R except E. ANP; Adenosine 5′-(β,γ-imido)triphosphate (PDB code:1jqh). A; *1. Imidazopyrazines*, X_2 = N, X_1 = CH, W = C, Z = H, X = O/N, acyclic ring; *2. Imidazotriazines*, X_2 = N, X_1 = N, W = C, Z = H or F, X = N, Y = CH; *3. Pyrrolopyrimidines*, X_2 = C, X_1 = N, W = N, Z = H, X = O, acyclic ring, B; Pyrrolopyrimidines, C; Pyrimidine/triazine-quinolines/naphthalenes, D; Isoquinolinediones, E; Hydantoin-quinolines, F; Cyanoquinolines, G; Benzimidazole-pyridones, H; Docking pose of thiazolidinediones in ATP-binding site.

Pyrrolopyrimidines

Blumenkopf *et al* of Novartis patented the class of pyrrolopyrimidines represented in Fig. (**3**) as Janus kinase inhibitors which find their applications in diabetes, cancer, and autoimmune diseases [201]. On the same track, Novartis developed and optimized the lead molecules, NVP-AEW541 and NVPADW742 as potent and selective IGF-1R inhibitors as compared to IR [202,203]. The compounds exhibited excellent *in vivo* activity against small cell lung cancer (SCLC) [204] and Ewing sarcoma cancer [205], and also provoked cell cycle arrest and apoptosis in multiple myeloma cells [206].

1	**2**
NVPADW742	**NVP-AEW541**
Cellular IGF-IR IC_{50} = 0.1-0.2 μM	Cellular IGF-IR IC_{50} = 0.086μM
Cellular IR IC_{50} 16 fold lower than above	Cellular IR IC_{50} = 2.3μM

Fig. (3). Pyrrolopyrimidines as IGF-1R inhibitors.

Afterwards Stanley *et al.* disclosed 4,6-bis-anilino-1*H*-pyrrolo[2,3-*d*]pyrimidines (**2**) as potent inhibitor of IGF-1R receptor tyrosine kinase [188], the concept of how the inhibition occurred, was further clarified after studying the crystallographic data of a docking model of the IGF-1R kinase domain in complex with pyrrolopyrimidine [38, 40,186]. Later on, a library of pyrrolopyrimidines (**3-8**) was generated *via* changing the substitution on general structure **2.1** as illustrated in Fig. (**4**). Initially the structural optimizations were done on C6 aniline where the substitution at C2' was found critical for efficient binding to IGF-1R as it is in spatially close proximity to Leu1051 of IGF-1R and has significant effect on the C6 aniline N-*H* pKa [207].

Pyrrolo[1,2,-*f*][1,2,4]triazines

A class of 2, 4-disubstituted pyrrolo-[1, 2-*f*][1,2,4]triazines as discussed in Fig. (**5**) was developed as IGF-1R inhibitor by Bristol Myers Squibb (BMS) after the lead optimization of **9**. SAR studies revealed that an aminopyrazole moiety, proline amide framework and the *S*-configuration of the above said compounds were critical and

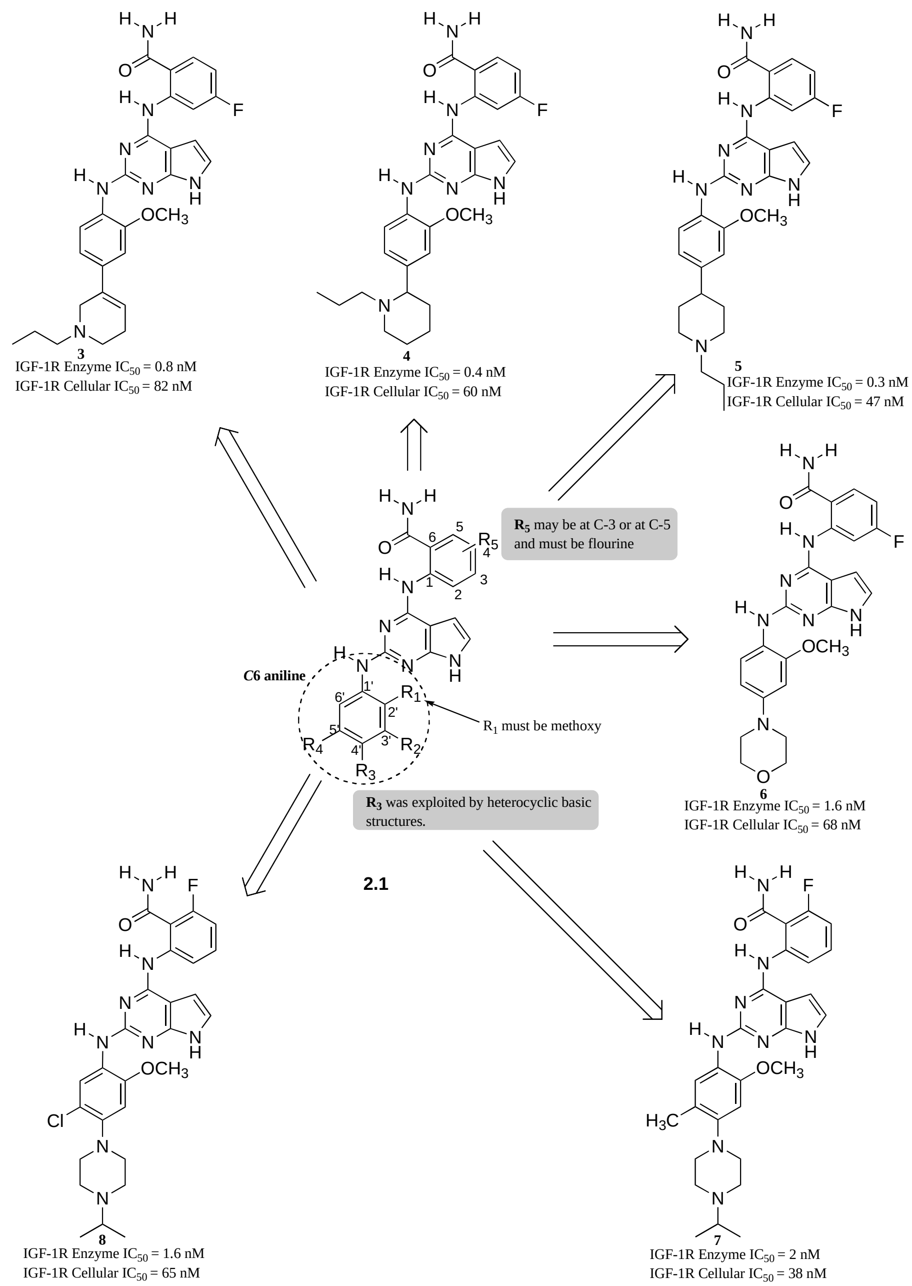


Fig. (4). SAR of some pyrrolopyrimidines.

responsible for the preferential selectivity towards IGF-1R inhibitory activity (**10-12**) [199]. X-ray co-crystal structure of **12** with IGF-1R throws light on the mode of fitting of flouropyridyl group *via H* bond with backbone amide of Asp1123 under the DFG motif located at the beginning of activation loop (PDB entry 3I81). The cyclopropyl group (**10**-**12**) exhibits interacts favorably with the gatekeeper residue Met1049 and catalytic Lys1003 than methyl group (**9**).

BMS further synthesized and screened various new compounds as shown in Fig. (**6**), based on the isosteric replacement of proline moiety with pyrrolidine (**13**), pyrrolidinone (**14**), acyclic (**15**) or carbocyclic (**16**) in between the fluropyridine and pyrrolotriazine of **12**. The 2º and 3º nature of amide and the spatial arrangement of amide connectivity between **13b** (*S*-isomer) and **13c** (*R*-isomer) were also found to be critical. As experimentally acyclic analog **15** was more potent than **13a**, it was concluded that cyclic proline isostere was not critical for kinase potency [193].

Pyrrolo[2,3-*b*]pyridines

Patnaik *et al* from GlaxoSmithKline recently reported 3,5-disubstituted -1*H*-pyrrolo[2,3-*b*] pyridines as IGF-1R inhibitors as depicted in Fig. (**7**) [187]. In exploring the SAR of this class, it was found that the *o*-phenoxy substructure (**17**) containing compounds were more selective for tyrosine kinase of IGF-1R as compared to tyrosine kinase of IR,

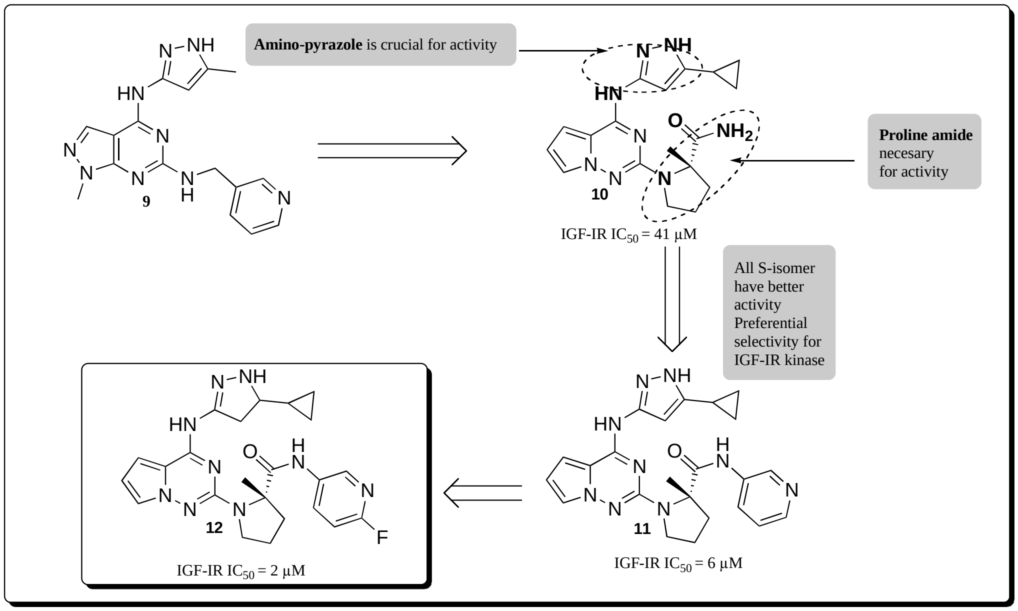


Fig. (5). Pyrrolo[1,2,-*f*][1,2,4]triazines as IGF-1R inhibitors.

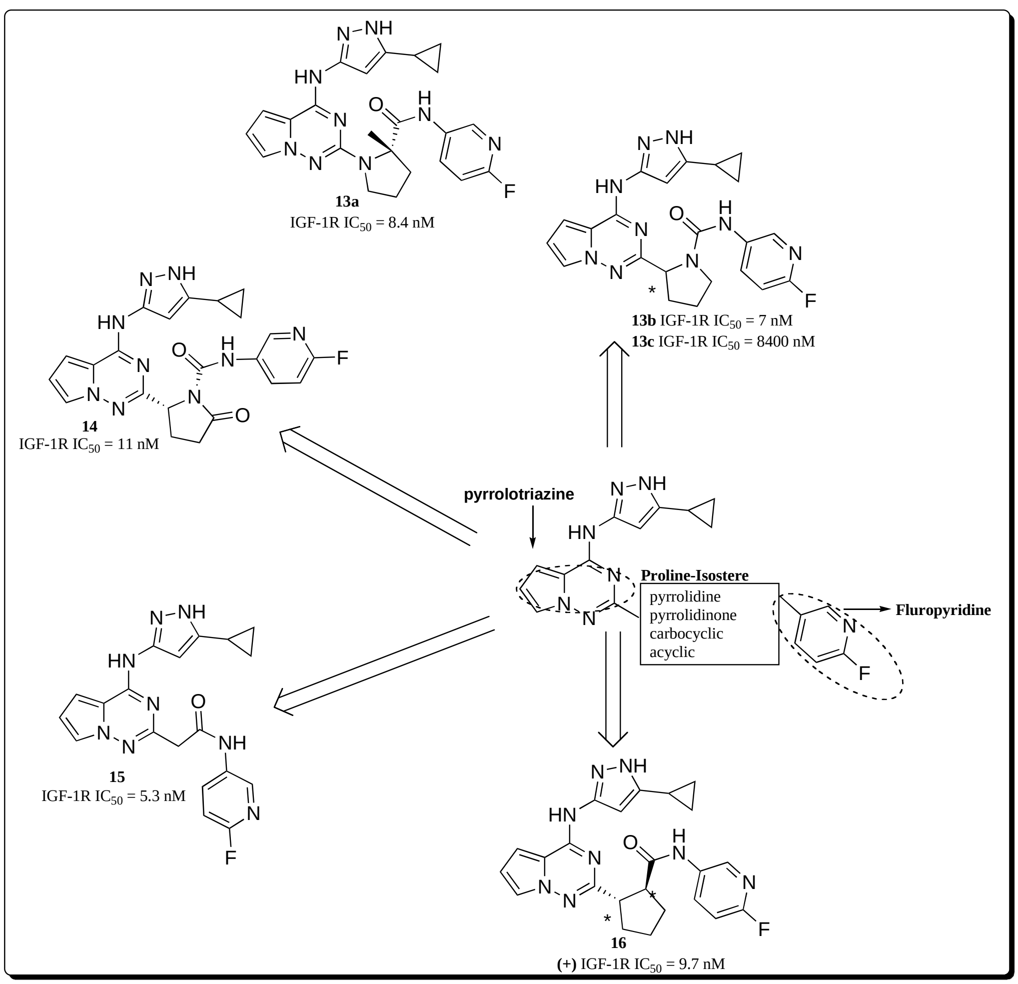


Fig. (6). Pyrrolotriazines and their isosteric modifications.

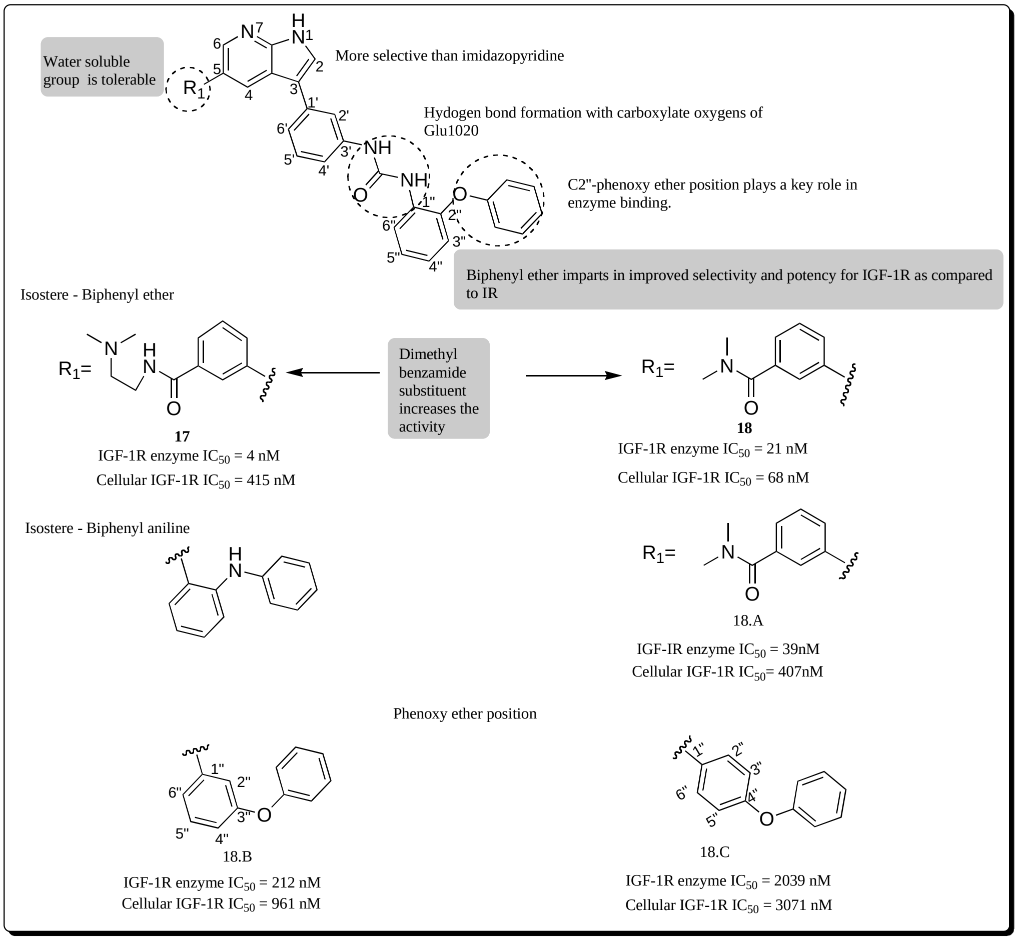


Fig. (7). Pyrrolo[2,3-*b*]pyridines and their SAR.

which encouraged them to retain this substructure in the exploration of the other derivatives of the class. SAR studies and reported X-ray co-crystal structure of the class revealed that (a) phenoxy substitutions at C-2`` is critical for inhibitory activity and selectivity for IGF-1R over IR (e.g. **17** and **18**), (b) isosteric replacement of phenoxy with aniline decreases the potency (compare **18** with **18.A**), (c) 1*H*-pyrrolo[2,3-*b*]pyridine core forms two *H*-bonds with kinase domain, one with carbonyl backbone of Glu1050 and second with the backbone amino group of Met1052, (d) C3 phenyl lies at inner hydrophobic region where it interacts with Val983, Leu1003, Met1049, Met1112 and Phe1124 and (e) C5 phenyl occupies the outer hydrophobic region with the ionizable 1° amine exposed to solvent.

Pyrazolo[3,4-*d*]pyrimidines

Abott laboratories designed 4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidines as multi-targeted inhibitors of IGF-1R, EGFR and Her-2 with IC_{50}s at nM level in a view to identify a single compound inhibiting the IGF-1R and its cross-talk mediated signaling with other receptor kinases [208,209]. The most potent compound of the class was screened against 80 kinases. The important binding interactions obtained from the docking experiments, and some key points of SAR studies are summarized in Fig. (**8**).

Imidazopyrazines/Imidazotriazines

OSI pharmaceuticals made efforts for the optimization of 8-amino-1,3-disubstituted–imidazo[1,5-*a*]pyrazine scaffolds (**19**) and led to the discovery of **20** as potent ATP-competitive IGF-1R inhibitors (Fig. **9**) which holds a key pharmocophoric donor/acceptor interactions with the kinase hinge region of IGF-1R as shown in Fig. (**2A**) [210]. Moreover, imidazo[1,5-*a*] pyrazine core has more benefits in comparison to conventional pyrrolo[2,3-*d*]pyrimidine core which includes a little reduction in the values of polar surface area (PSA), log D and log P. Together all these parameters provide an edge by increasing the flexibility in attachment selection. Further lead optimization and DMPK profiling of **20** led to the discovery of novel molecules such as AQIP [211], PQIP [212], OSI-906 [213], **21** [214] and 4-aminoimidazo[5,1-*f*][1,2,4]triazine-derived FQIT. Later on, FQIT was explored and disclosed as dual IGF-1R and IR inhibitor in the treatment of cancer [215].

Imidazo[1, 2-*a*]pyridines

In 2009, GlaxoSmithKline disclosed imidazo[1, 2-*a*]pyridines as IGF-1R inhibitors at nanomolar concentration [216]. During the development of SAR of the compounds, the following key points were observed as represented in Fig. (**10**): (a) reversal orientation of the amide connectivity

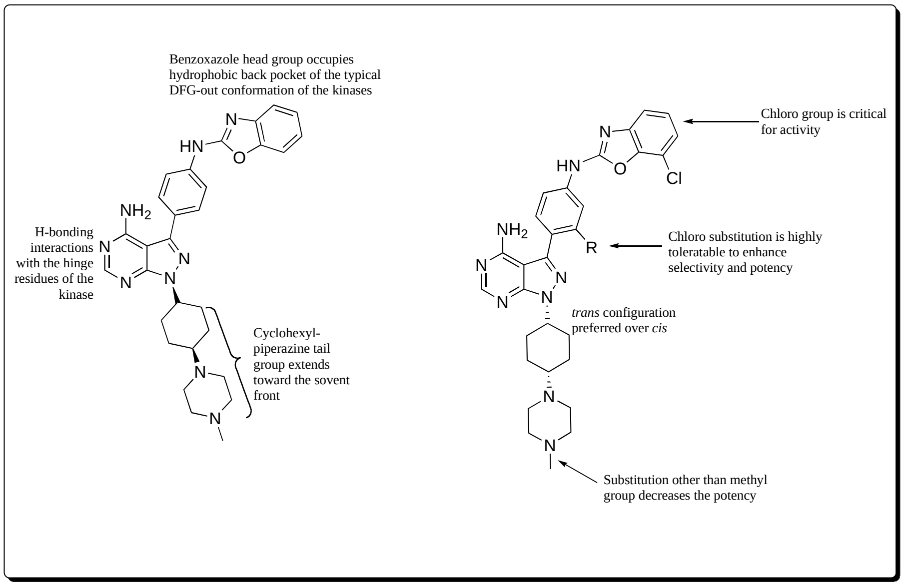
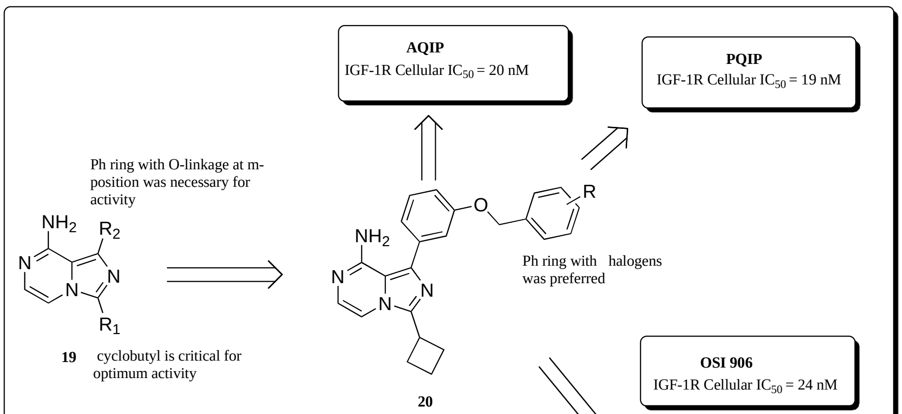
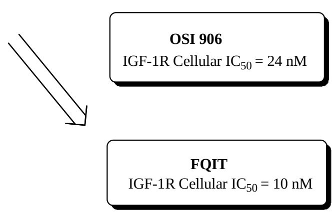
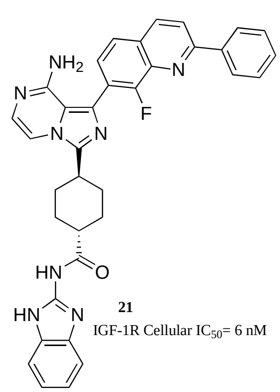


Fig. (8). Pyrazolo[3,4-*d*]pyrimidines and their SAR.





	R	IGF-IR IC_{50} (μM)	Cellular IC_{50} (μM)
20.1	H	0.606	1.16
20.2	2-fluoro	0.224	2.06
20.3	3-fluoro	0.510	3.29
20.4	2,3-Difluoro	0.898	5.69
20.5	2,5-Difluoro	0.329	9.76
20.6	2,6-Difluoro	0.215	1.59
20.7	2-cholro-6-fluoro	0.248	2.67



21
IGF-1R Cellular IC_{50}= 6 nM

Fig. (9). Lead optimization and SAR of imidazopyrazine/imidazotriazines.

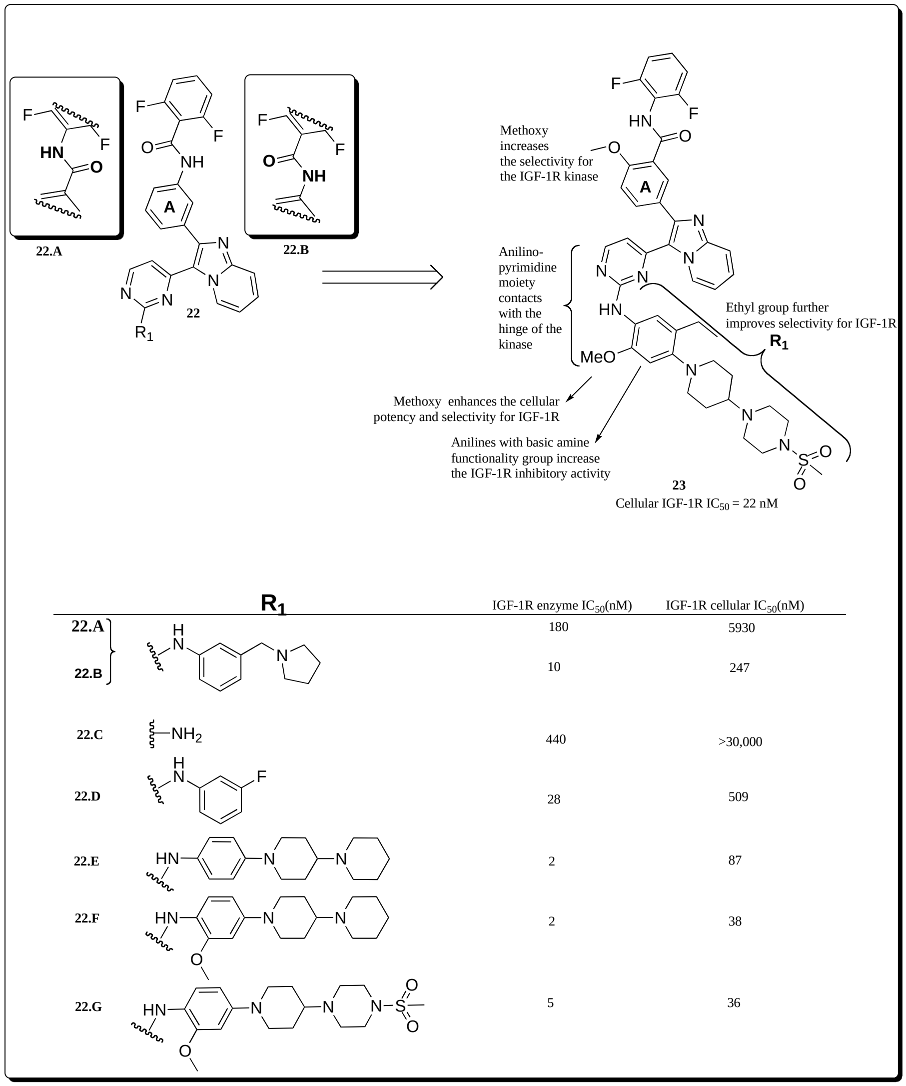


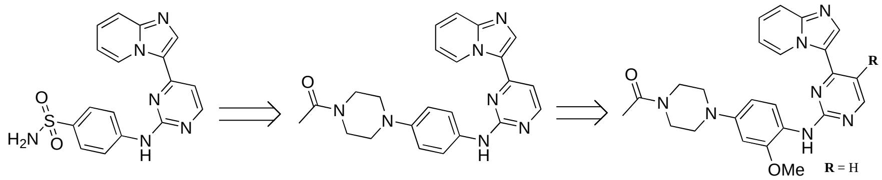
Fig. (10). Imidazo[1, 2-*a*]pyridines and their SAR.

was critical for the activity (compare **22.A** with **22.B**), (b) substitutions at R_1 such as aniline (**22.D**) or its derivatives bearing 2-methoxy group (**22.F** and **22.G**-methoxy group enhances cellular potency and selectivity for IGF-1R), morpholine or bipiperidine moieties (**22.E-G**) were found to be important as compared to amino group (**22.C**) and (c) introduction of *o*-methoxy group at the ring A enhances IGF-1R inhibitory activity (**23**). The proposed binding mode of 23 dictates the various interactions such as (a) bidentate hinge *H*-bond between anilinopyrimidine moiety and Glu1050 and Met1052 and (b) piperazino-piperidine moiety occupying the solvent exposed region.

In 2011, AstraZeneca modified their earlier reports of imidazo[1, 2-*a*]pyridines as cyclin dependent kinase (CDK) inhibitors [217,218] and screened them through cellular and enzymatic IGF-1R high throughput screening protocol [219]. Compound **24** was identified as hit molecule as shown in Fig. (**11**). Lead optimizations of **24** such as replacement of *p*-sulfonyl group with *N*-acetylpiperidine (**25**) led to the decrease in CDK and increase in IGF-1R inhibitory activities. Further, introduction of *o*-methoxy group imparted in enhancement in IGF-1R selectivity over CDK (**26**) due to its steric interaction with Phe-82 of CDK-2 [217]. Exploitation of C5 position of the pyrimidine ring of **26** by putting electron withdrawing groups such as chloro and bromo (**27** and **28**, respectively), resulted in further increase in the IGF-1R activity due to the lipophilic interactions of the halogens with the gatekeeper residue of IGF-1R. Various positions of the imidazopyridine ring of **27** were substituted with halogen, methyl, methoxy, amino or cyano groups, but none of the modification led to the enhancement of IGF-1R activity as shown in Fig. (**12**). Compound **27** emerged as dual inhibitor of IGF-1R and IR (enzyme IC_{50} = 9 nM, Cellular IC_{50} = 12 nM). It was further optimized to get **43** as shown in Fig. (**13**) for increasing its oral absorption by replacement of *N*-acetyl piperazine ring and affinity for hERG ion channel to reduce cardiac arrhythmia in the patients [220].

Benzimidazole-pyridone

In 2005 Bristol-Myers Squibb (BMS) disclosed ATP-competitive inhibitors of IGF-1R kinase domain possessing benzimadazole-pyridone pharmacophore. The first hit of the

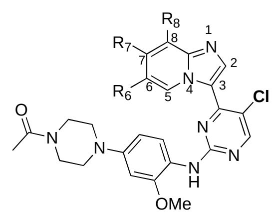


24 **25** **26**

	24	**25**	**26**
IGF-1R IC_{50} (μM)	1.26	0.27	0.45
CDK-2 IC_{50} (μM)	0.001	0.078	more than 100

	27	**28**	**29**	**30**
R	Cl	Br	Me	OMe
IGF-1R IC_{50} (μM)	0.010	0.003	0.047	0.090
CDK-2 IC_{50} (μM)	1.1	1.1	10	53
Cellular IC_{50} (μM)	0.017	0.009	0.092	0.19

Fig. (11). Optimization of imidazo[1,2-*a*]pyridines.



27

	Flouro			**Methyl**			**Methoxy**					
	31	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**
$\mathbf{R_6}$	H	H	F	H	H	CH_3	H	H	OCH_3	NH_2	CH_2OH	CN
$\mathbf{R_7}$	H	F	H	H	CH_3	H	H	OCH_3	H	H	H	H
$\mathbf{R_8}$	F	H	H	CH_3	H	H	OCH_3	H	H	H	H	H
IGF-1R IC_{50} (mM)	0.010	0.011	0.007	0.013	0.009	0.010	0.040	0.008	0.055	0.035	0.035	0.14
Cellular IGF-1R IC_{50} (mM)	0.022	0.025	0.013	0.038	0.026	0.013	0.11	0.043	0.066	0.054	0.11	0.77

Fig. (12). Imidazo[1,2-*a*]pyridines with different substitutions.

class was **44** [221]. X-ray structure of **44** in complex with kinase domain of IGF-1R (Fig. **2G**) indicated the binding interactions and scope of substitution of methyl group of imidazole ring and substitution at C4 position of pyridone to further explore and access the open ribose binding pocket of the active site. Much attention was paid to substitute C4 position as shown in Fig. (**14**) with hydroxy derivative of phenylethylamine to get more potent **45.** In order to maintain the optimum balance between CYP-450, IGF-1R inhibitory activity and oral bioavailability of **45**, its imidazole ring was replaced with morpholine and this resulted in two enantiomers **46** (BMS-536924; *S*-form; IC_{50} = 100 nM) and **47** (*R*-form; IC_{50} = 830 nM) [192,222,223]. BMS-536924 was found better tolerated than alloxan-induced hypoinsulinemia and more effective than metformin in the treatment of experimental insulin-responsive breast cancer [224]. The same research group in 2006 reported **48** (BMS-554417) as the lead compound after substitution of the imidazole ring with piperazine of **45** [225]. In the year 2008, **49** (BMS-695735) was disclosed with improved ADME properties including CYP 3A4 induction and inhibition, broad spectrum *in vivo* antitumor activity and minimal drug-drug interactions as compared to **46** [226]. Further, BMS research group put major emphasis on structure activity and structure solubility studies of **46** that led to discovery of BMS-577098 (**50**) [227].

Pyrimidines/Triazine-quinolines/Naphthalenes

In 2011 Buchanan *et al* disclosed bisarylamino-1,3-pyrimidine/traizines as IGF-1R inhibitors [195]. The screening of the compounds provided an observation that pyridine core was preferred over triazines as shown in Fig. (**15**) (compare **52** and **55** with **51** and **56**, respectively) which was evidenced by the X-ray crystal structure (Fig. **2C**). The -*CH*-(in pyrimidine) in place of -*N*-(in triazine) increased the

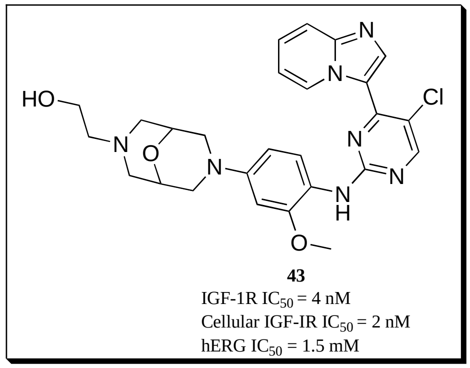


Fig. (13). 43 as IGF-1R inhibitor.

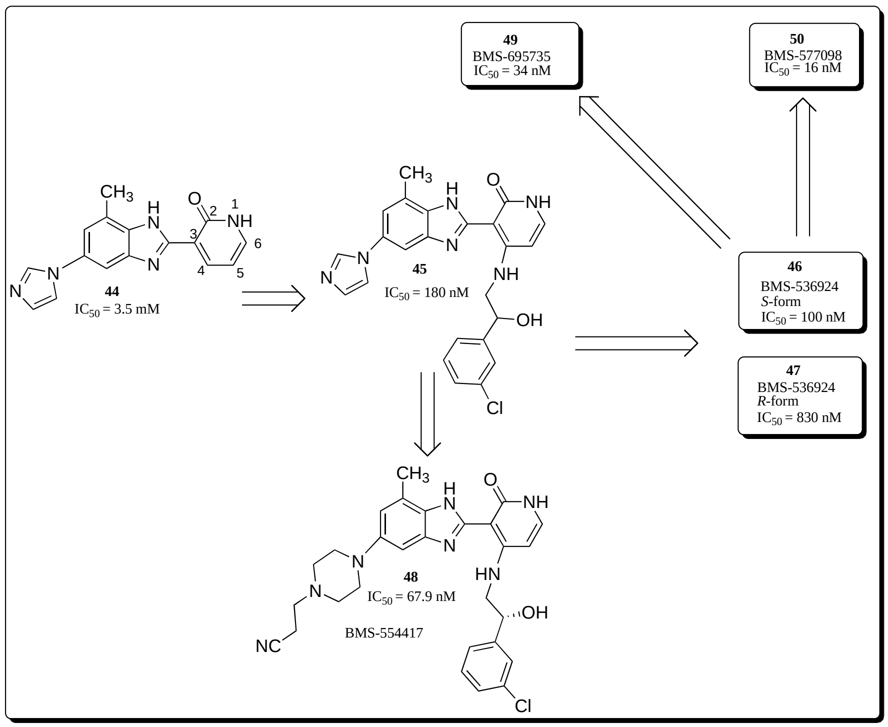


Fig. (14). Discovery of Benzimidazole-pyridones as IGF-1R inhibitors and their SAR.

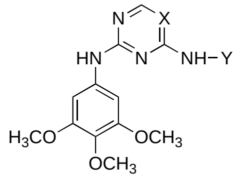
hydrophobic compatibility with the adjacent environment of gatekeeper Met1079 residue of the cleft i.e. better interaction with the kinase of IGF-1R. The importance and effects of methoxy, quinoline and morpholine (occupying solvent front region) on the activity have been illustrated in Fig. (**15**) and (**16**). Further ADME profiling of the synthesized compounds provided **57.6** as the best molecule which was orally tolerable and having *in-vivo* antitumor activity in a mouse calu-6 tumor xenograft model.

Isoquinolinediones

Wyeth research group performed a high throughput screening by using Lance enzyme assay where 5359 hits were generated. It was appeared by SAR as shown in Fig. (**17**) and X-ray structure as illustrated in Fig. (**2D**) that (a) basic amine functional group in the tailpiece region of the molecule was crucial for inhibitory activity and (b) the compound exhibited basic interactions with hydrogen bond acceptor/donor/acceptor triad of kinase domain. The Library analogs showed that many different tertiary amines including *N*-methyl piperazine were tolerable at this position (**58**) [191].

Cyanoquinolines

Wyeth research group in 2009 reported 3-cyanoquinolines as IGF-1R inhibitors (**59;** Fig. (**18**)) [190], which were effective at nanomolar concentration in cancer treatment and proved to be better agents as compared to a series of isoquinolinedione [191]. SAR and X-ray crystal structure (**Fig 2F**) highlighted the role of chloro at C3’, 2-thio-imidazole head piece at C4’ of aniline ring and basic amine (like *N*,*N*-dimethyl amino, piperazine, pyrrolidine, morpholine derivatives) at C7 position in governing the IGF-1R inhibitory activity. **60** emerged as the best obtained [190], but unfortunately the selectivity ratio (IR-IC_{50} inhibition / IGF1R-IC_{50} inhibition) for **60** was 0.17.



Key points of SAR studies

(i) Biological screening evaluated the pyrimidine better scaffold than triazine

(ii) Further substitutions were done on pyrimidine pharmacophore

(iii) Quinoline when replaced with isoquinoline-moderate changes were seen in activity

(iv) If quinoline is linked at *C*6 position rather than *C*3, both enyzmatic or cellular activity increases by 5-10 folds (compare **51** with **54**)

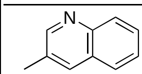
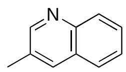
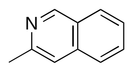
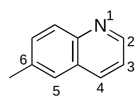
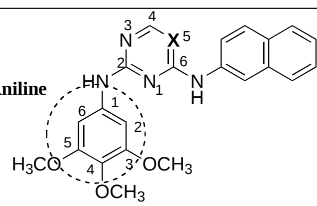
	Y	X
51		X = N IC_{50} = 41 nM Cellular IC_{50} = 175 nM
52		X = CH IC_{50} = 2.5 nM Cellular IC_{50} = 19 nM
53		X = CH IC_{50} = 5.2 nM Cellular IC_{50} = 14 nM
54		X = CH IC_{50} = 3.3 nM Cellular IC_{50} = 37 nM

Fig. (15). Triazines and pyrimidines as IGF-1R inhibitors and their SAR.

Aniline



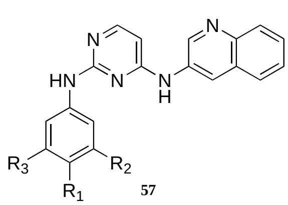
Key points of SAR studies

(i) Aniline can be explored at *C*-3,*C*-4 and *C*-5 position

(ii) Morpholine or piperidine at R_1 is better suited to tailor ADME properties

55
X = N
IC_{50} = 13 nM
Cellular IC_{50} = 409 nM

56
X = CH
IC_{50} = 2.2 nM
Cellular IC_{50} = 88 nM



57

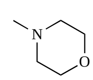
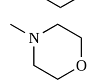
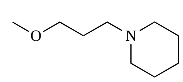
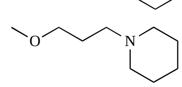
	R_1	R_2	R_3	Enzymatic IGF-1R IC_{50}	Cellular IGF-1R IC_{50}
57.1	OCH_3	OCH_3	H	18 nM	507 nM
57.2	OCH_3	H	OCH_3	20 nM	6453 nM
57.3	OCH_3	H	H	55 nM	1783 nM
57.4	H	OCH_3	H	40 nM	1044 nM
57.5		H	H	22 nM	177 nM
57.6		OCH_3	H	2.4 nM	8.4 nM
57.7		H	H	19 nM	81 nM
57.8		OCH_3	H	3.8 nM	36 nM

Fig. (16). Triazines and pyrimidines and their SAR.

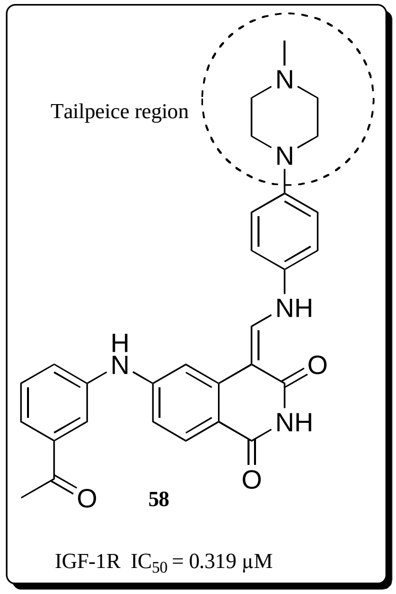


Fig. (17). Isoquinolinedione as IGF-1R inhibitor.

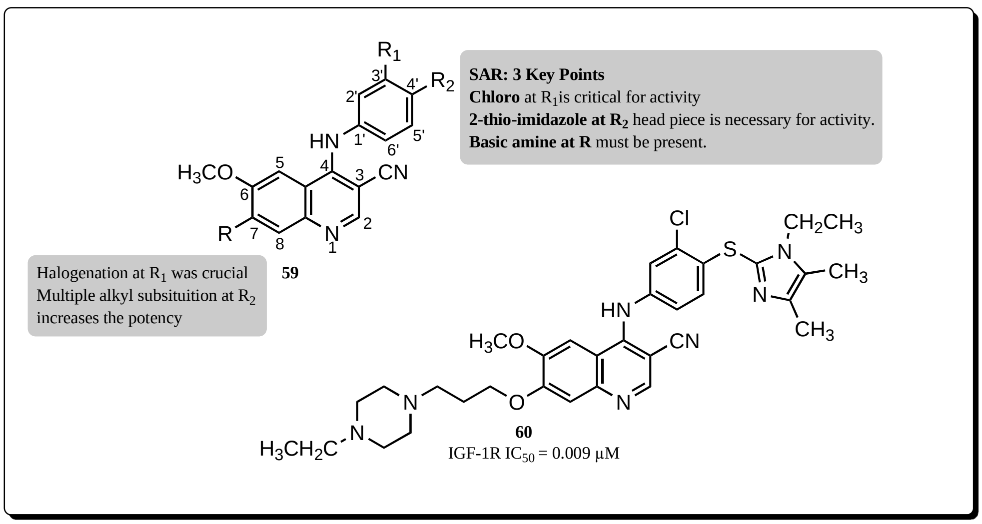


Fig. (18). Cyanoquinolines and their SAR.

Aryl Heteroaryl Ureas/Diaryl Ureas

These were synthesized and evaluated [228], as potent IGF-1R kinase inhibitors on the breast cancer cell line MCF-7 [229] that led to **61** as the lead compound. Further optimizations of **61** produced more potent derivatives (**61.1**, **61.2**, **61.3**) [230]. The salient features of the class have been mentioned in Fig. (**19**).

Indole-hydrazides (Fig. 20)

In 2011 Schmidt *et al* discovered oxoacetohydrazide derived *N*'-aroyl-2-(1*H*-indol-3-yl)-2-oxoacetohydrazide as dual IGF-1R/Src inhibitors at sub-micromolar level [231]. Compounds **62** and **63** were found to be potent dual inhibitors of IGF-1R and Src. The docking of the compounds revealed that tert-butyl or ethoxy groups occupy in the large pocket of IGF-1R and Src and may be responsible for the selectivity. However the X-ray structure may actually throw light on the key interactions with kinase domain as well as on the type of inhibition of the class of the compounds.

Indole based- allosteric Inhibitors

While parallel screening of a series of indole -and tetrahydrocarbazole- based compopunds against aurora-A kinase and other RTKs by Buttner *et al.* in 2010 **64** and **65** were obtained as the leads against IGF-1R which were taken further for optimization. The mechanism of inhibition was clarified by measuring the IC_{50} values in presence of ATP and it was finally concluded that there was no effect of ATP concentration on the inhibition i.e. the inhibition was independent of the ATP concentration indicating a non-ATP competitive (allosteric) mechanism involved [232]. The SAR studies indicated some key points which are demonstrated in Fig. (**21**).

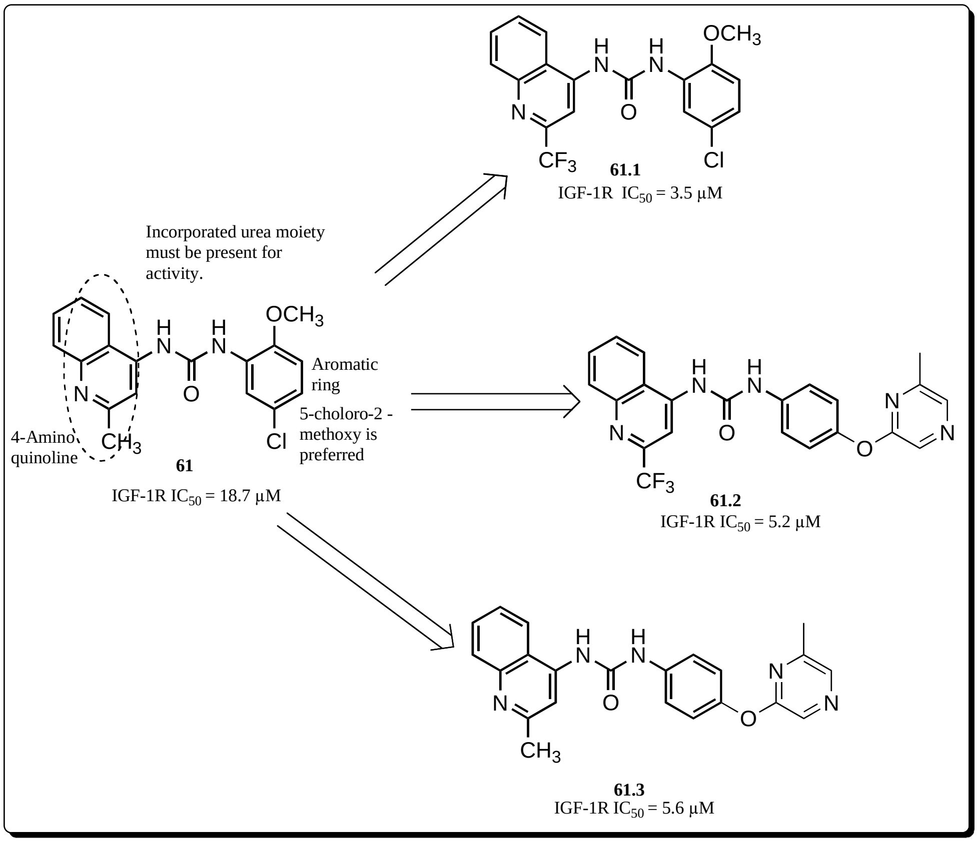


Fig. (19). Aryl herteroaryl ureas and SAR.

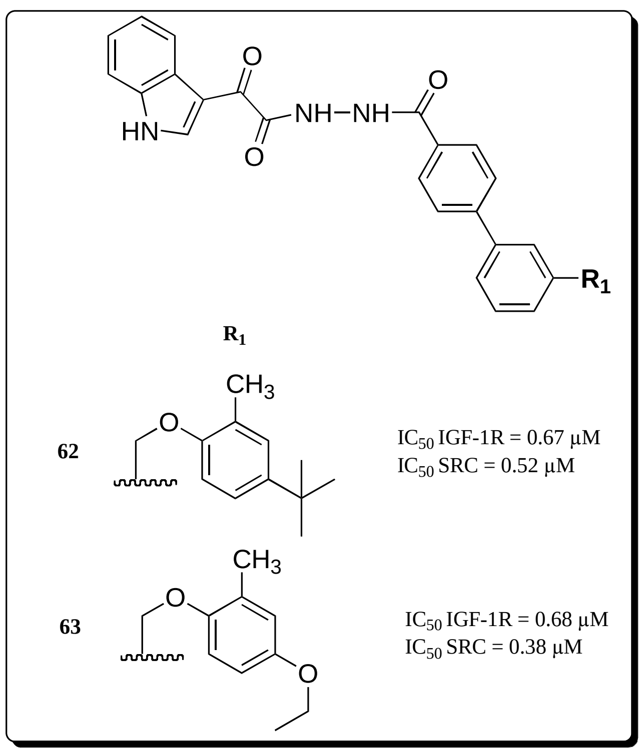


Fig. (20). Indole-hydrazides and their SAR.

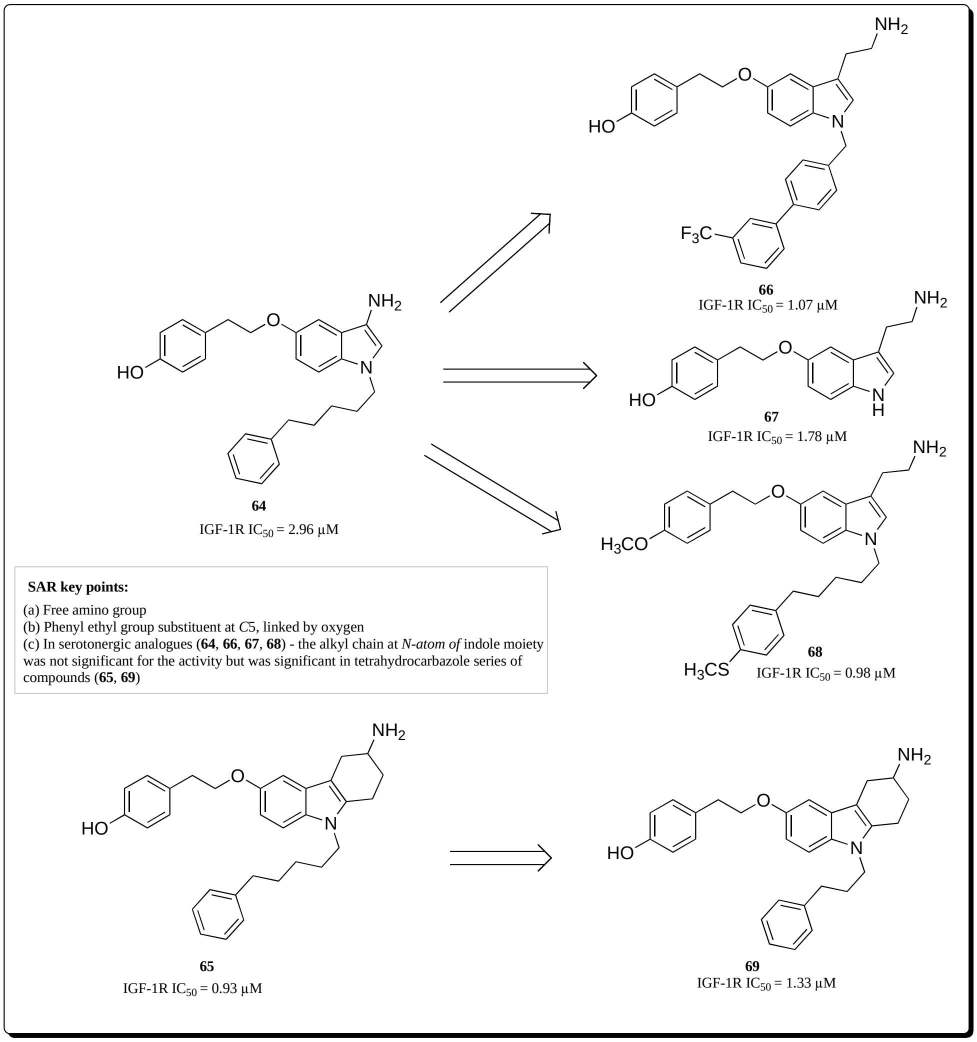


Fig. (21). Indole based allosteric inhibitors and their SAR.

Indole Alkylamines

Heinrich *et al.* disclosed the SAR and X-ray crystal structure of indole alkylamines (Fig. (**22**) and (**23**); **70**-**77**) as allosteric inhibitors of IGF-1R. The findings revealed that (a) 5-nitrile group was found in the H-bond distance to a water molecule located in the interface of the side chain of Lys1033 and Glu1050 and the backbone carbonyl of Phe1047, (b) indole N*H* donor functionality, (c) *n*-butyl chain on one side made van der Waals interactions to the side chains of amino acid residues (Met 1054, His 1133, Ile 1151, and Phe 1131), on the other side it made a contact with large cluster of water molecules, (d) two water molecules of the cluster assisted in H-bonding between *N*-atom of piperidine and side chain of Asp 1153. From the biochemical point of view, this class when tested for cellular activity against phospho-IGF-1R and the conclusion was made from observation that these compounds do not influence IR signaling significantly up to concentrations of 30 µM [198].

Thiazolidinediones

Thiazolidinediones in 1990 were reported as tyrosine kinase inhibitors for EGFR and c-Src by Geissler *et al.* [233]. Thiazolidine-2,4-diones are also well-known anti-diabetics as they target the nuclear receptor, PPAR-γ (peroxisome proliferator-activated receptor-γ) [234], among them several are FDA approved and for other activities such as inhibitors of PI3K-γ [235,236] HIV-1 entry protein gp41 [237] and Pim kinase family [238]. Recently, Liu *et al*. disclosed, thiazolidinedione as IGF-1R inhibitors through hierarchical virtual screening followed by *in-vivo* assay. **78** and **79** emerged as lead scaffolds which were further exploited to discover **80** and **81** and to identify the key points of SAR and docking pose as discussed in Fig. (**24**) and Fig. (**2H**), respectively [239].

Hydantoins

Lesuisse *et al* reported first non-ATP competitive IGF-1R kinase inhibitors (Fig. (**25**) and (**2E**)) by initiating a high throughput screening against IGF-1R and finally ended up with a hit **82** (azaindole) [196], which was then further optimized by combinatorial chemistry and then chemically modified to get **83** (IC_{50} was identified by an autophosphorylation-HTRF assay with a non-phosphorylated recombinant GST-IGF-1R protein) [197].

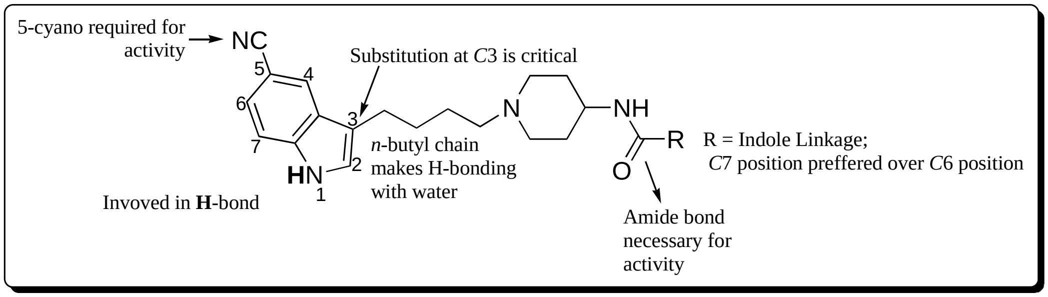


Fig. (22). SAR of indole alkylamines.

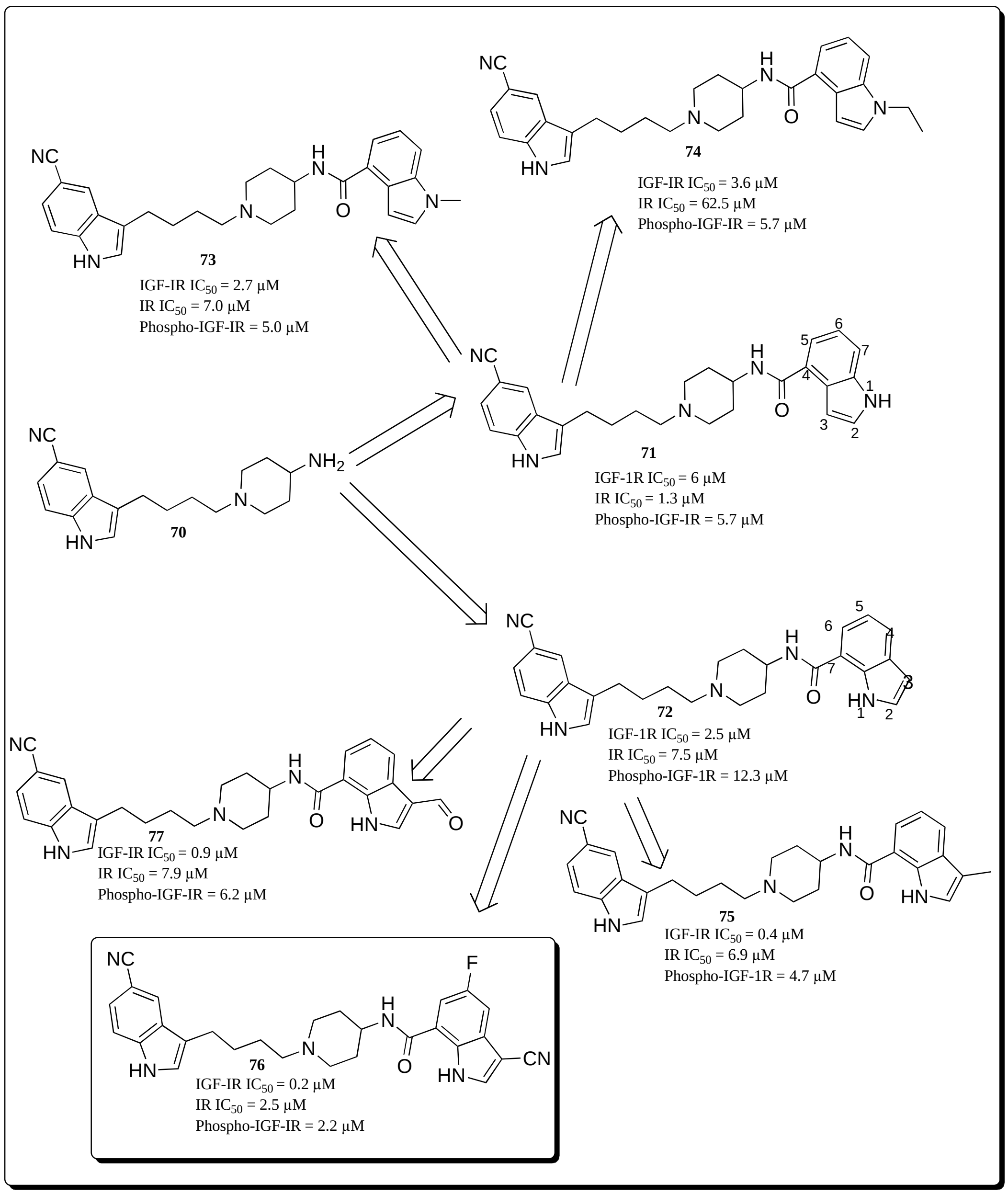


Fig. (23). Indole alkylamines as IGF-1R inhibitors.

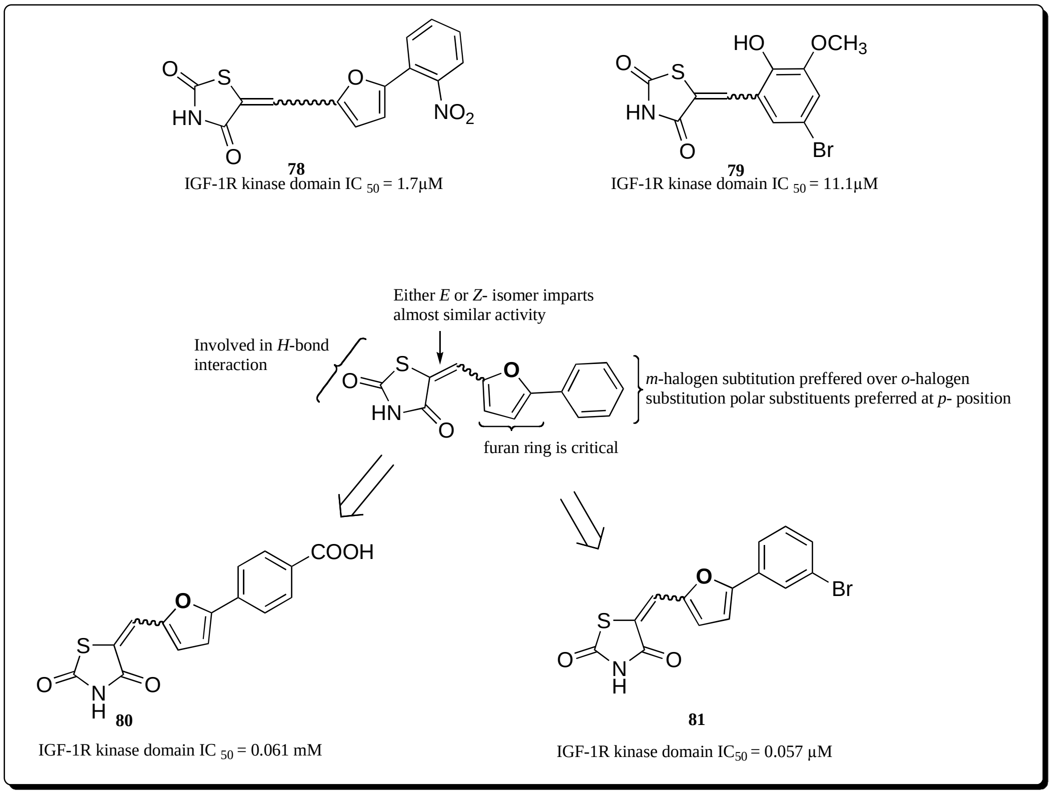


Fig. (24). Thiazolidinones and their SAR.

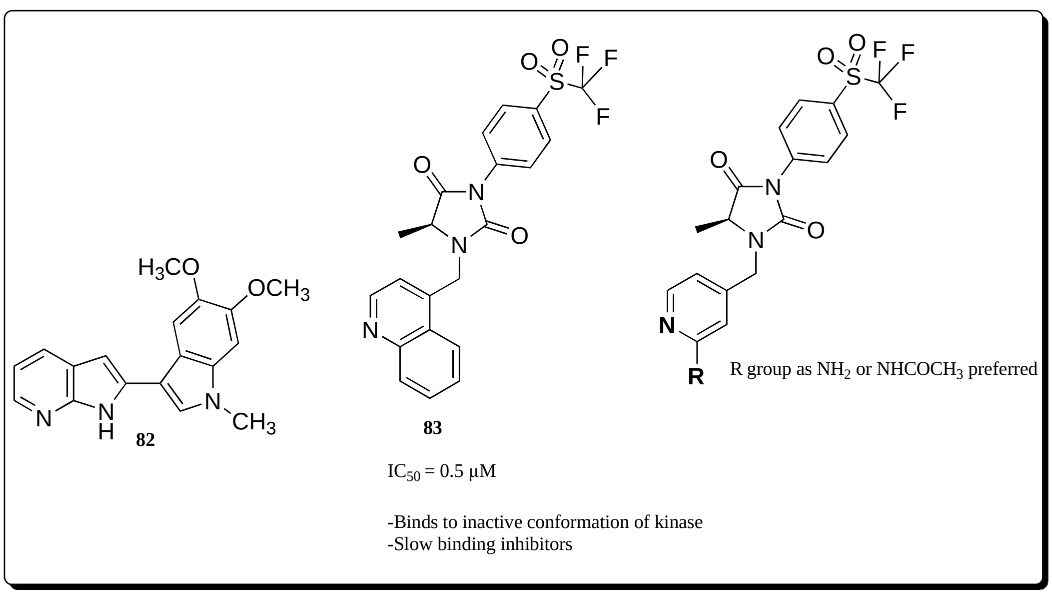


Fig. (25). Hydantoins and their SAR.

Oxafluorenes

In 2010, Krug *et al.* disclosed 1-aza-9-oxa-fluorenes, as IGF-1R inhibitors [240], after screening them against the panel of RTKs (Fig. **26**). Some of the compounds were active against EGFR and VEGFR2 also. In order to find the basis of potency against IGF-1R, EGFR and VEGFR2, docking of the class was done in the above mentioned kinases and following conclusions were drawn: (a) 1-aza-9-oxa-fluorene mimics the adenine ring of ATP and represents a hinge-binding motif, (b) *H*-bond formation occurs between *N*-atom of pyridine and the backbone N*H* of the hinge residue Met793 (EGFR), Met1082(IGF-1R) and Cys919 (VEGFR2), (c) The R group interacts with the hydrophobic pocket adjacent to gatekeeper residue (Thr790) in EGFR,

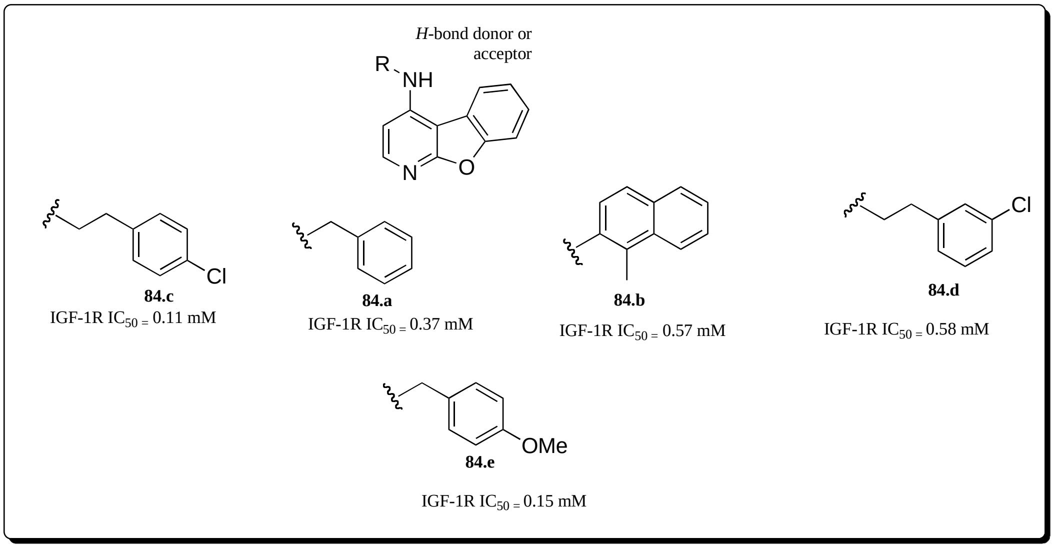


Fig. (26). 1-Aza-9-oxa-fluorenes as IGF-1R inhibitors.

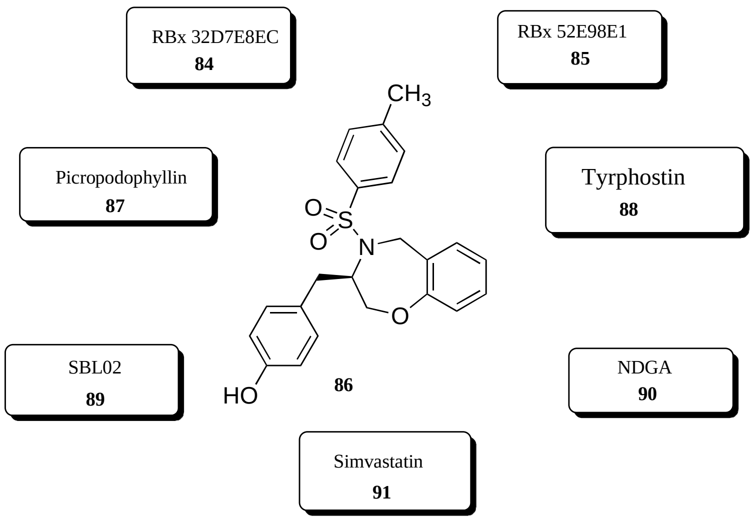


Fig. (27). Miscellaneous compounds as IGF-1R inhibitors.

Met1079 in IGF-1R and Thr916 in VEGFR2), (d) Varying size of gatekeeper residue and the hydrophobic pocket are mainly responsible for the respective kinase selectivity (e) Hydrophobic groups are better tolerated in this pocket while polar groups remains out of this pocket and (f) nevertheless IGF-1R possesses the more hydrophobic methione as gatekeeper resulting in higher affinities for higher hydrophobic groups (**84.c**, **84.d**).

Miscellaneous (See Fig. 27)

In 2011 Tandon *et al* described the dual and synergistically working EGFR/IGF-1R inhibitors **84** and **85** to overcome the resistance associated with single target inhibitor [241]. In 2011 Chakravarti *et al*. reported benzoxapine **86** and investigated its in-vitro and *in-vivo* effects in IGF-1R mediated estrogen dependent breast cancer cells (MCF-7 and MDA-MD-231) [242]. Picropodophyllins (**87**) also called cyclolignans, a different class which doesn't involve competitive ATP inhibition, rather interferes with autophosphorylation of the IGF-1R were reported [243, 244]. **87** showed activity in the IGF-1R mediated cancerous cell lines and regression of cancerous cells, in the mice bearing the xenografted human tumor cells which were taken from the human tumor cell lines (PC-3 prostate cancer cell lines, ES-1 Ewing sarcoma cell lines and BE malignant melanoma cancer cell lines) [245]. This compound proved some superiority over the other classes as it showed less resistance [246]. AG538 (**88**) a class tyrphostins which came at 1980's are derived from benzylidene malonitrile and possesses the catechol structure and IC_{50} in cell free kinase assay at 61 nM, but doesn't bind to the ATP binding site [44,160]. Attempts were made to derivatise the catechol moiety to obtain the metabolically stable compounds to oxidation [160]. SBL02 (**89**), a non ATP-competitive inhibitor having structural similarity to AG538 indicating the significance of catechol pharmacophore in non ATP-competitive inhibitor of IGF-IR with IC_{50} of 170 nM in cell free kinase assay was reported [247]. Non-dihydroguiretic acid (**90**) a potent antioxidant obtained from a natural source creosote bush (*Larrea divaricata*), was reported to increase the age of the male mice but not the female ones [248,249]. It inhibits IGF-1R signaling, cell growth and cell survival of neurolastoma in human cells [250]. Later on it was found that **90** inhibits the IGF-1R signaling in androgen depending growth of the LAPC-4 prostate cancer cell line s [251]. Simvastatin (**91)** inhibits HMG-CoA reductase subsequently decreasing the dolichyl phosphate (non-sterol isoprenoid derivative of mevalonate pathway (NIDMP) which is responsible for *N*-glycosylation of proteins. NIDPMP is also necessary for IGF-1R to target to the plasma membrane to become functional receptor, ultimately decreases the plasma membrane expression of IGF-1R [252,253]. This attributes of N-glycosylation had been used to down regulate the IGF-1R at cell surface and assisted to stop signaling in Ewings sarcoma cell, which finally leads to the death of the cells[254]. Heat shock protein 90 (HSP 90) inhibitors [255,256] inhibit the proteins which are involved in the regulation, folding and unfolding of the other proteins and in mediating the membrane targeting of IGF-1R [256, 257, 181, 258, 259].

FUTURE PROSPECTIVE

There has been a shift in the cancer chemotherapy paradigm from classical to advance level after the discovery of tyrosine kinase inhibitors. Currently, small molecules IGF-1R inhibitors are under scrutiny for their development as anticancer agents in various phases of preclinical and clinical stages. Resistance and toxicities issues as observed in the other TKIs are likely to be noticed only when some clinically approved candidates come into the market. However, the issues can be resolved by structure based drug design of more potent ATP-competitive inhibitors based on the key interactions guided by X-ray crystal structures of IGF-1R in complex with inhibitors and SAR of the reported pharmacophores. The design of allosteric inhibitors is considered to be safer and more effective as compared to competitive inhibitors due to their higher affinity towards mitogenic dominant receptor (IGF-1R) as compared to diabetogenic dominant (IR) receptor [198]. Additionally, the concept of designing of irreversible inhibitors *via* covalent binding could be a smart and significant approach to selectively target mutant type IGF-1R as observed in case with other kinase inhibitors. Some medicinal chemists have the opinion that dual inhibition of IGF-1R and IR is rational [260]. On the contrary, cancer patients treated with such inhibitors will be susceptible to have diabetic condition. Thus design of a dual inhibitor of IGF-1R and selective IR-A could be a better and alternate approach as IR isoform-IR-A is recommended to be mitogenic in nature. Multi targeting of IGF-1R with some other receptors involved in the cross-talk cancer progression either by a single or multi inhibitors appears to be a useful strategy to provoke the synergistic effect leading to decrease in resistance.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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ABBREVIATIONS

ADMET	=	Absorption, distribution, metabolism, excretion and toxicity
ATP	=	Adenosine triphosphate
BMS	=	Bristol-Myers Squibb
EMT	=	Epethelial mesechymal transition
GDP	=	Guonosine diphosphate
GRB	=	Growth factor receptor bound protein
GSK	=	Gycogen synthetase kinase
GTP	=	Guonosine triphosphate
IGF-1	=	Insulin-like growth factor-1
IGF-1R	=	Insulin-like growth factor-1 receptor
IR	=	Insulin receptor
IRS	=	Insulin receptor substrate
PI3K	=	Phosphoinostitol-3 kinase
PIP_2	=	Phosphatidylinositol 4, 5-biphosphate
PIP_3	=	Phosphatidylinositol 3,4,5-biphosphate
RTK	=	Receptor Tyrosine Kinase
RTKI	=	Receptor Tyrosine Kinase Inhibitors
SAR	=	Structure activity relationship
TK	=	Tyrosine Kinase

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