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Original article

Cyclopentyl-pyrimidine based analogues as novel and potent IGF-1R inhibitor

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ABSTRACT

A series of novel 2-amino-4-pyrazolecyclopentylpyrimidines have been prepared and evaluated as IGF-1R tyrosin kinase inhibitors. The *in vitro* activity was found to depend strongly on the substitution pattern in the 2- amino ring, 4-pyrazolo moieties and size of fused saturated ring with the central pyrimidine core. A stepwise optimization by combination of active fragments led to discovery of compound **6f** and **6k**, two structures with IGF-1R IC_{50} of 20 nM and 10 nM, respectively. **6f** was further profiled for its anti cancer activity across various cell lines and pharmacokinetic studies in Sprague Dawley rats.

1. Introduction

Insulin-like growth factor receptor (IGF1R) is a transmembrane receptor tyrosin kinase. The IGF signalling cascade involves interactions between receptors, ligands, binding proteins, and downstream enzymes. Upon ligand binding, it's known to activate two signalling pathways of great importance in cancer biology, the Pi3K-AKT-mTOR pathway and the Ras-Raf-MEK pathway [1]. Dysregulation of the IGF-IR signalling pathway have been implicated in the development of many types of tumours, including colon, breast, pancreatic, multiple myeloma, and sarcoma [2,3]. Insulin-like growth factors and their receptor tyrosine kinase, IGF-IR, have been involved in the development and progression of cancer, by contributing towards proliferative, antiapoptotic, and proangiogenic signalling. Agents that inhibit IGF-IR activity at the receptor level may be useful in treatment of various cancers [4,5].

Various methods of inhibition of IGF-1R have been evaluated to bring about a desired clinical response. A plethora of monoclonal anti-bodies are in various stages of clinical trials. These antibodies are IGF-1R specific and are thus extremely useful tool to evaluate the clinical relevance of IGF-1R inhibition. As compared to mAbs there are relatively fewer small molecule IGF-1R inhibitors in various stages of clinical trials. The most advanced of them, Linsitinib (OSI906), a Phase III clinical candidate from OSI Pharmaceuticals [6], is presently being evaluated for adrenocortical carcinoma. It is also undergoing preclinical evaluation as either a single agent or in combination with various other anti-cancer agents. Though only a few of these inhibitors are being evaluated in clinical trials, there are multiple scaffolds known as IGF-1R inhibitors. OSI-906 is imidazo[1,5-a]pyrazines scaffold [7,8]. Various other scaffolds like benzimidazoles [9–13], 3-cyanoquinoline [14,15], isoquinolinedione [16], Pyrrolo-[1,2-f][1,2,4]triazine [17], 2,4-bis-

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arylamino-1,3-pyrimidines [18] have been reported in the literature. A hydantoin core as a non ATP competitive IGF-1R inhibitor [19] has also been reported by Buchanan et al. In addition to these scaffolds imidazo[1,2-α]pyridines [20–22] and 1H-pyrrolo[2,3-b] pyridines [23–25] have also been reported from various pharmaceutical companies as IGF-1R inhibitors. The concept of allosteric inhibition as IGF-1R inhibitors have also been explored [26].

2. Chemistry

2.1. Design of compounds

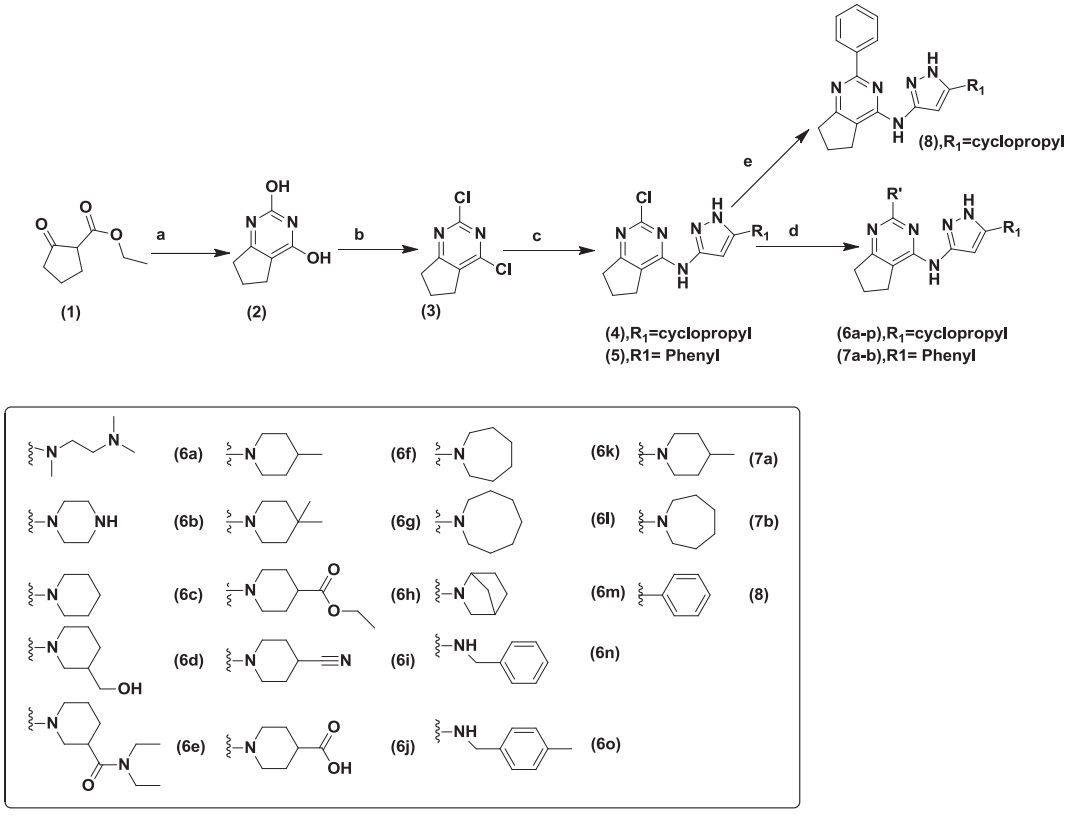
In a quest to discover a new class of IGF-1R inhibitors our group focused upon the discovery of a cyclopentyl-pyrimidine scaffold. The rational for the design of a cyclopentyl-pyrimidine core was a combination of factors to generate a novel core and was primarily driven by docking studies. Herein we report detailed SAR of the cyclopentyl-pyrimidine scaffold and its optimization to result in a low nM IGF-1R inhibitor. Using a classical approach for inhibiting kinases we planned on choosing a hinge-binding motif. Based on literature precedence we planned to decorate the cyclopentyl-pyrimidine core with a 5-cyclopropyl-1H-pyrazol-3-amine to introduce hinge binding capabilities. This amino pyrazole moiety has been used as a hinge binding motif in other kinase inhibitor programs. The designed compounds were validated by docking studies. The docked compounds were compared to the co-crystallized ligand of a pyrrolo-[1,2-f][1,2,4]triazine based compound (BMS754807 from Bristol Myers Squibb), in terms of docked conformations, hinge interactions, hydrophobic interactions, active site occupancy and also for unfavourable contacts [27].

2.2. Synthesis of target compounds

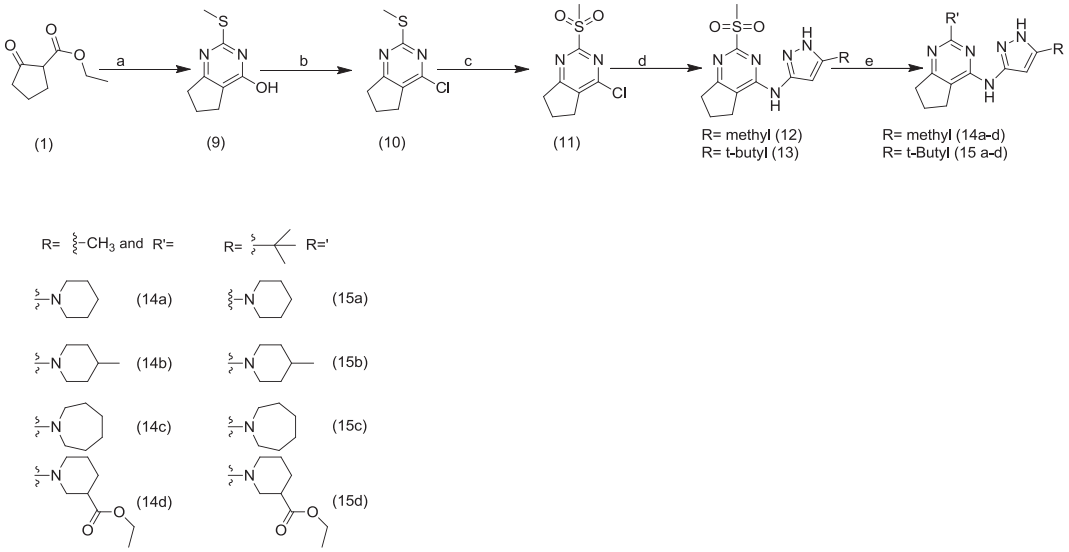
The synthesis of the desired analogs were executed via a four step parallel synthesis protocol as explained in Schemes 1–3. To investigate the importance of 4-methyl piperdine, a series of 2-substituted pyrimidine analogs (**6a-6o, 7a-b, 8**) were synthesized as described in Scheme 1. The key precursor of cyclopentyl dichloropyrimidine (**3**) was obtained from dihydroxy pyrimidine (**2**) upon treatment with $POCl_3$. The dihydroxypirimidine was obtained from commercially available corresponding beta-ketoesters (**1**), via initial cyclisation with urea [28]. The key intermediate, cyclopentyl dichloropyrimidine (**3**) was selectively substituted with 5-cyclopropyl-1H-pyrazol-3-amine and 5-phenyl-1H-pyrazol-3-amine at the 4-chloro position, to build-in the desired hinge binding motif thus yielding **4** and **5** respectively. The 2-chloro of the pyrimidine (**4** and **5**) reacted under much harsher conditions to facilitate a detailed SAR. Using this synthetic scheme derivatives **6a**–**6o** and **7a**–**b** were synthesized [29]. Compound **8** was synthesized by the treatment of 2-chloropyrimidine (**4**) with phenyl boronic acid under microwave condition (Scheme 1).

3. Results and discussion

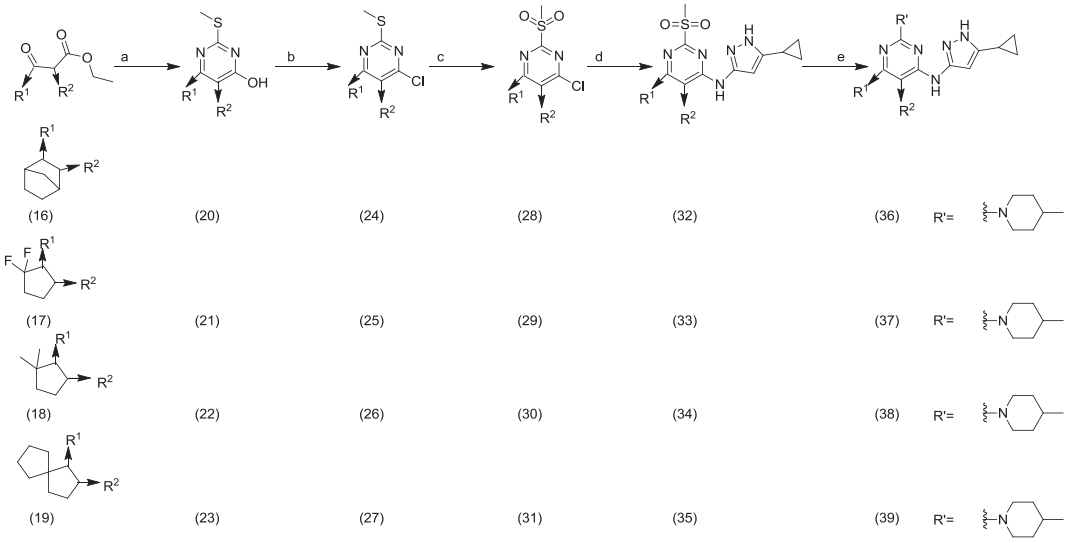
The first set of SAR was focused on the 2-chloro position of the pyrimidine core to identify the best substitution at that site. The initial SAR set included amino substitutions of the chloro group. The chloro moiety was substituted with aliphatic amine (**6a**), piperazine (**6b**), piperidine (**6c**) and substituted piperidines (**6d**–**6j**). The piperidine substitution (**6c**) yielded excellent IC_{50} of 32 nM Table 1. Compound **6c** when docked exhibited 3 hinge H-



Scheme 1. Reagents and conditions: (a) Urea, Cat. HCl, ethanol, 80 °C, 5 h (b) $POCl_3$, 110 °C, 12 h (c) Et_3N, 5-cyclopropyl-1H-pyrazol-3-amine (for compound 4)/5-phenyl-1H-pyrazol-3-amine (for compound 5), 80 °C ethanol, 48 h (d) corresponding amine, NEt_3, IPA, 180 °C, 12 h sealed tube (e) $PhB(OH)_3$, $Pd(PPh_3)_4$, $NaHCO_3$, DME, 180 °C, 55 min, microwave.



Scheme 2. Reagents and conditions: (a) 2-Methyl-2-thiopseudourea hemisulfate salt, $NaHCO_3$, H_2O, overnight (b) $POCl_3$, 110 °C, overnight (c) m-CPBA, DCM, RT, 12 h (D) 5-cyclopropyl-1H-pyrazol-3-amine, DMF, NEt_3, 110 °C, 12 h (e) corresponding amine, NEt_3, NMP, 160 °C, 20 min, microwave.

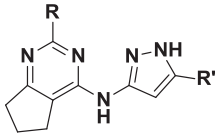


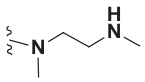
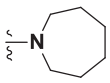
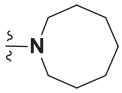
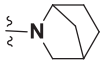
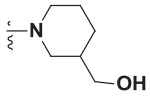
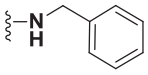
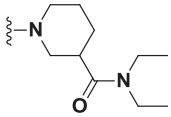
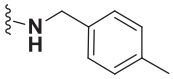
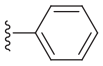
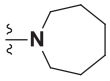
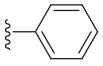
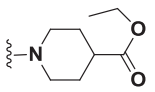
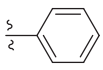
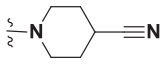
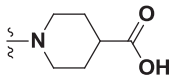
Scheme 3. Reagents and conditions: (a) 2-Methyl-2-thiopseudourea hemisulfate salt, $NaHCO_3$, H_2O, overnight (b) $POCl_3$, 100 °C, overnight (c) m-CPBA, DCM, RT, 12 h (d) 5-cyclopropyl-1H-pyrazol-3-amine, DMF, NEt_3, 110 °C, 12 h (e) corresponding amine, NEt_3, NMP, 160 °C, 20 min, microwave.

bonds between the pyrazole ring nitrogens and hinge residues, Glu1050 and Met1052, as observed for the literature compound, BMS754807. Hydrophobic interactions were observed for the cyclopropyl group with Met1049 (gatekeeper residue), Ala1001, Met1126 residues. The piperidine moiety of **6c** did not enter the groove but does generate hydrophobic interactions with Met1126 to some extent resulting in the observed activity. Based on these encouraging results we explored further to obtain a better piperidine derivative by substituting it at 3 (**6d,6e**) or 4 positions of the piperidine ring (**6i,6h,6f,6g,6j**). These compounds were screened in IGF-1R assay. Compounds with substitutions at the 3rd position turned out to be active. Hydroxyl group in compound **6d** showed an H-bond with Gln977 backbone thus exhibiting good potency. Substituted amide in **6e** occupied the groove but due to its steric bulk, it had unfavourable contacts leading to deteriorated potency. Hydrophobic substitutions at the 4th position were favourable as it extended piperidine ring into the groove such as in 4-methylpiperidine derivative (**6f**, Fig. 1) that resulted in improved activity of 20 nM in IGF-1R enzyme assay. However adding another methyl at the same position (**6g**) made it sterically bulky and did not fit into the pocket thus rendering it less active. Azapane (**6k**) and Azocane (**6l**) derivatives were synthesized to evaluate the piperidine ring size. Expanded rings **6k** and **6l** generated hydrophobic interactions with Met1126 and Val983 due to their three dimensional character. This was also observed with bridgehead substitutions as in **6m** resulting in equivalent potency. Besides cyclic aliphatic groups, aromatic systems were also evaluated (**8, 6n, 6o**). Direct phenyl ring substitution (**8**) in place of piperidine reduced hydrophobic interactions due to planar non 3D conformation resulting in reduced activity. Insertion of a linker (**6o**) positioned the compound well into the pocket and gained on hydrophobic interactions.

The SAR around the 2-position of the pyrimidine core led to the identification of a 4-methylpiperidine and an azapane moieties with low nM IC_{50} in IGF-1R enzyme assays Table 1.

Table 1
Biochemical evaluation of compound **6a**–**8** in IGF-1R assay.



Compd.	R	R′	IC_{50}-IGF1R (μM)	Compd.	R	R′	IC_{50}-IGF1R (μM)
(6a)			>1	**(6k)**			0.01
(6b)			>1	**(6l)**			0.058
(6c)			0.032	**(6m)**			0.041
(6d)			0.09	**(6n)**			0.267
(6e)			0.184	**(6°)**			0.149
(6f)			0.02	**(7a)**			>1
(6g)			0.203	**(7b)**			>1
(6h)			0.035	**(8)**			0.097
(6i)			0.124	OSI-906			0.002
(6j)			>1				

At this point in the SAR journey, the cyclopropyl pyrazole motif was subjected to a reevaluation. A scan of methyl **14a**–**d**, tertbutyl **15a**–**d** Table 2 and phenyl substitutions **(7a** and **7b)** at the 5-position of the pyrazole reemphasized cyclopropyl being the best tolerated moiety at this site with low nM IC_{50} in IGF-1R. Methyl substitution in place of cyclopropyl reduced hydrophobic interactions leading to a drop in activity for all the compounds. Tertbutyl substitutions showed hydrophobic interactions but close contacts were observed due to its steric bulk leading to drop in potency compared to cyclopropyl analogs. The methyl and tertbutyl substituted pyrazole compounds when subjected to the synthetic route as described in Scheme 1 led to low synthetic yields. Thus different synthetic routes (Scheme 2) for the synthesis of the desired analogs were developed. A four step parallel synthesis protocol was adopted (Schemes 2 and 3). Typically all β-ketoesters **(16**–**19)** were synthesized by treatment of corresponding ketone with diethyl carbonate in presence of sodium hydride to yield S–Me-4-hydroxy pyrimidine **(9, 20**–**23)**. The 4-hydroxy was converted to the 4-chloro moiety (**10**, **24**–**27**) using the conventional $POCl_3$ condition [30]. Subsequent to that, the 2-methylthio moiety **(10, 24**–**27)** was oxidized to the 2-methylsulfonyl moiety **(11, 28**–**31)** [31]. The 4-chloro was functionalized with methyl and tertbutyl animopyrazoles (**12**–**13**). The 2-position of the pyrimidine core was subsequently functionalized to obtain desired compounds for further SAR evaluation (**14a**–**d**, **15a**–**d**) (Scheme 2). Synthesis of new chemical entities around the cyclopentyl core ring structure was obtained following the synthetic strategy devised in Scheme 2. The 4-chloro of pyrimidine moiety (**28**–**31**) was functionalized with cyclopropyl aminopyrazole (**32**–**35**). The 2-position methylsulfonyl group (**32**–**35**) was displaced by 4- methyl piperidine to obtain products **36**–**39** for further SAR (Scheme 3).

SAR efforts were then focused towards optimization of the core ring structure. Cyclopentyl ring faced the solvent front thus expanding the ring size to bicyclic fused ring further extended the hydrophobic group unfavourably into the solvent and also pushed the compound towards the polar hinge protein backbone. Due to similar reasons, a bicycle fuzed structure 5,6,7,8-tetrahydro-6,8-methanoquinazolin core, (**36**) also led to significant loss of

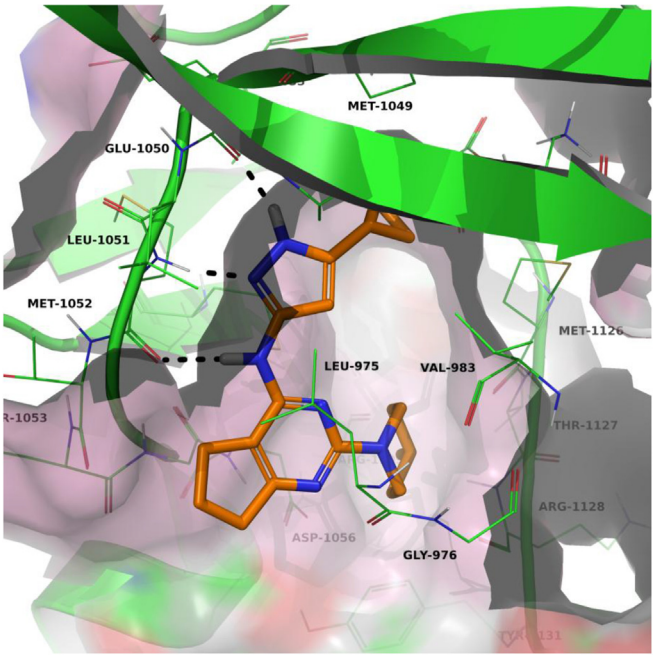


Fig. 1. IGF-1R binding site interactions of **6f** showing hinge H-bonds, methyl-piperidine ring entering into the small groove in the interior of the pocket.

primary activity Table 3. A flip in the docked conformation of the bicyclic ring was observed. Small lipophilic substitution of the cyclopentyl ring with fluorines (**37**) also led to significant loss of IGF-1R activity. A dimethyl substitution instead of fluorines led to a greater loss in IGF-1R activity. A dihydrospiro-cyclopenta[d]pyrimidine-7,1′-cyclopentan (**38**) core also led to a significant loss of enzyme activity. Thus the cyclopentyl-pyrimidine core structure seemed to be an optimal core structure. A detailed SAR based on their *in-vitro* activity led to the identification of compound **6f** as the most optimized compound with a potential to be advanced forward. With these encouraging results for compound **6f** in *in-vitro* assays it was subjected to cell proliferation assays across a short panel of relevant cell lines.

Compound **6f** was screened for its ability to inhibit cancer cell proliferation across a panel of cell lines for lung, colon, and breast (Table 4) cancers. Compound **6f** exhibited good potency across a few cell lines in lung cancer. It exhibited a potency of 180 nM in H460 cell line while it was found to be 340 nM in A431 cell line. Even in colon cancer cell line compound **6f** exhibited 350 nM IC_{50}. Triple negative breast cancer being an unmet disease area, compound **6f** was tested against triple-negative breast cancer cell line (MDA-MB231) where it exhibited a moderate activity of 700 nM. It's IC_{50} in MCF-7 was on a higher side of 1.67 μM. Owing to IGF-1R's homology to Insulin receptor (IR) almost all IGF-1R small molecule inhibitors also inhibit IR. Only monoclonal antibodies are known to be selective IGF-1R inhibitors. Thus we screened this compound in IR biochemical assay. Compound **6f** exhibited an IC_{50} of 110 nM. It is well known in the literature that a dual IGF-1R and IR inhibitor may have adverse pharmacological effects of hyperglycemia. There is a certain school of thought which encourages the need of a selective IGF-1R inhibitor over IR while others advocate a more multikinase approach with equipotent inhibition of IGF-1R and IR for a more pronounced anti-cancer effect. Encouraged with moderate selectivity of IGF-1R over IR we choose **6f** for further pharmacokinetic profiling.

Absolute oral bioavailability studies were performed in Sprague Dawley rats. Compound **6f** exhibited low absolute oral bioavailability of 11.3%. It turned out to be a low absorption compound with high i.v. clearance of 3548 mL/h/kg. Thus for these compounds to be subjected to animal studies, improvement in ADME profile was imperative Table 5.

4. Conclusion

A novel cyclopentyl-pyrimidine based IGF-1R inhibitor with excellent *in vitro* and cell based activity was discovered as promising template for the development of a more druggable IGF-1R inhibitor. This compound also exhibited moderate selectivity over IR, an attribute which might have safety related advantages in the clinic. The most advanced compound exhibited moderate oral exposure in Sprague Dawley rats. An extensive medicinal chemistry program will be necessary to address pharmacokinetics related issues. The simple synthetic procedures and plausible docking mode of **6f** in IGF-1R are good arguments to consider such a development campaign.

5. Experimental section

5.1. Chemistry

Unless otherwise specified all reagents were obtained from Aldrich and solvents were obtained from Thomas Baker and used without further purification. ^{1}H NMR spectra were recorded on a Bruker spectrometer (300 MHz) and (500 MHz) using either $CDCl_3$ or DMSO-d6 as the solvent. Chemical shifts, δ, are reported in ppm relative to the solvent peak. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants, J, are reported in Hertz. Mass spectral (MS) data were obtained on a Bruker Daltonics spectrometer using an electrospray ionization-quadrapole-time of flight (ESI-QTOF) analyzer. All melting points have been determined on a manually operated Veego (VMP-1) melting point apparatus and are reported uncorrected. HPLC purities have been determined for the final compounds using a Waters Alliances 2695 system implementing the following method for chromatographic separation.

5.1.1. HPLC method

Elution with 20–80% linear gradient of acetonitrile in 6 min followed by 20–80% linear gradient of 0.01 M NH_4OAc +0.5% TEA, pH 5.0 with AcOH in 1 min that is continued using an isocratic elution with 80% 0.01 M NH_4OAc +0.5% TEA, pH 5.0 with AcOH for 3 min using a Ascentis TM Express (50 × 4.6 mm I.D.), 2.7 mm operated at 1 ml/min and detection at 288 nm.

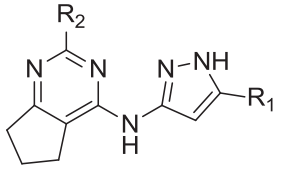
5.2. General procedure for the synthesis of compounds **4** and **5**

A solution of compound **3** (1.7 g, 8.99 mmol), an appropriate pyrazol-3-amine (360 mg, 9.89 mmol) and triethylamine (1.88 ml, 13.49 mmol) in EtOH (25 ml) were stirred at room temperature for 48 h. Solvent was removed under reduced pressure and the residure was extracted in EtOAc. The organic layer was washed with water and dried over anhydrous sodium sulphate, filtered and concentrated to yield **4** and **5** as a solid. **4** and **5** were used without for further purification for the next step.

5.2.1. 2-Chloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (**4**)

Grey Solid: Yield 40%, mp 170 °C. ^{1}H NMR (300 Hz, DMSO-d_6): δ 0.68 (d, 2H, J = 3.6 Hz, cyclopropyl-CH_2), 0.92 (d, 2H, J = 6.6 Hz, cyclopentyl $-CH_2$), 1.85–1.90 (m, 1H, cyclopropyl $-CH$), 1.95–2.05 (m, 2H,cyclopentyl $-CH_2$), 2.69–2.78 (m, 4H, cyclopentyl $-CH_2$), 6.27 (s, 1H, pyrazole $-H$), 9.58 (s, 1H, pyrazole $-$NH), 12.14 (s, 1H, pyrimidine $-$N*H*).

Table 2
Biochemical evaluation of compound **14a**–**15d** in IGF-1R assay.



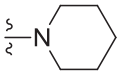
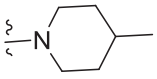
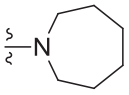
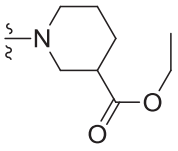
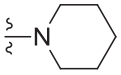
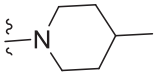
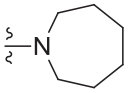
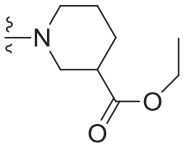
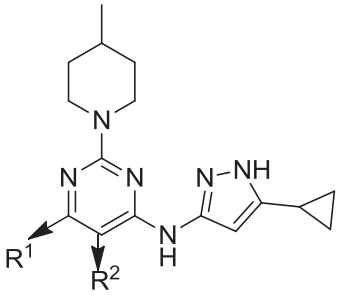
Compd.	R1	R2	IC50-IGF1R (μM)
(14a)			0.442
(14b)			NA
(14c)			~2
(14d)			0.97
(15a)			0.251
(15b)			0.3
(15c)			0.568
(15d)			0.108

Table 3
Biochemical evaluation of compound **36**–**39** in IGF-1R assay.



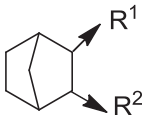
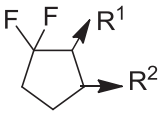
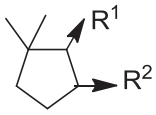
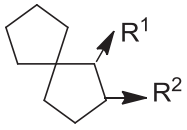
Compd.	R^1/R^2	IC_{50}-IGF1R(μM)
(36)		1.19
(37)		0.786
(38)		1.5
(39)		2.8

Table 4
Compound **6f** in CGI assay across various cell lines.

Lung (IC_{50} μM)			Colon (IC_{50} μM)		Breast (IC_{50} μM)	
H460	H-1975	A-431	HCT-116	Colo205	MDA-MB-231	MCF-7
0.18	3	0.34	0.35	2.19	0.7	1.67

*5.2.2. 2-Chloro-N-(5-phenyl-1H-pyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (**5**)*

Brown Solid: Yield 53%, mp 165 °C. ^{1}H NMR (300 Hz, DMSO-d_6): δ 1.96–2.06 (m, 2H, cyclopropyl $-CH_2$), 2.72 (m, 4H, cyclopropyl $-CH_2$), 6.93 (s, 1H, Ar–*H*), 7.30–7.35 (m, 1H, Ar–H), 7.44 (t, 2H, J = 7.5 Hz, Ar–H), 7.70 (d, 2H, J = 7.5 Hz, Ar–H), 9.76 (s, 1H, pyrazole –N*H*), 12.95 (bs, 1H, pyrimidine –N*H*). ESI-MS *m*/*z*: 310.0.

*5.2.3. General procedure for the synthesis of compounds **6a**–**6p** and **7a**–**b***

An appropriate amine (0.399 mmol) and triethyl amine (0.253 ml, 1.813 mmol) were added to a stirred solution of **4** (0.100 g, 0.363 mmol) in isopropyl alcohol (5 ml) at room temperature in a sealed tube. The mixture was heated at 180 °C for 12 h, and then cooled to room temperature. The reaction mixture was evaporated and crude mass was poured onto water (10 ml) and extracted with EtOAc (3 × 10 ml). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude residue, which was purified by silica gel column chromatography using CH_2Cl_2/MeOH (100/1 to 100/10) as eluent to obtain the solid products.

*5.2.3.1. N4-(5-cyclopropyl-1H-pyrazol-3-yl)-N2-(2-(dimethylamino) ethyl)-N2-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (**6a**).* White Solid: Yield 52%, mp 170 °C. ^{1}H NMR (300 Hz, $CDCl_3$): δ 0.74–0.77 (m, 2H, cyclopentyl $-CH_2$), 0.89–0.97 (m, 2H, cyclopentyl $-CH_2$), 1.87–1.92 (m, 1H, cyclopentyl $-CH$), 2.03–2.13 (m, 2H, cyclpentyl $-CH_2$), 2.37 (s, 6H, N^1,N^1,N^2-trimethylethane – 1,2-diamine $-CH_3$), 2.64 (dd, 4H, cyclpropyl $-CH_2$), 2.80 (t, 2H, J = 7.5 Hz, – N^1,N^1,N^2-trimethylethane – 1,2-diamine $-CH_2$), 3.19 (s, 3H, N^1,N^1,N^2 – trimethylethane –1,2 – diamine $-CH_3$), 3.80 (t, 3H, J = 6.9 Hz, N^1,N^1,N^2 – trimethylethane –1,2 – diamine–CH_2), 5.99 (s, 1H, pyrazole –N*H*), 6.70 (s, 1H, pyrazole –N*H*). HRMS (*m*/*z*) calcd. for $C_{18}H_{28}N_7$ $[M+H]^+$: 342.2401; found 342.241; HPLC Retention time – 1.31 min, Purity – 98.82%.

*5.2.3.2. N-(5-cyclopropyl-1H-pyrazol-3-yl)-6,7-dihydro-2-(piperazin-1-yl)-5H-cyclopenta[d]pyrimidin-4-amine (**6b**).* White Solid: Yield 52%, mp 147.1–148.8 °C. ^{1}H NMR (300 Hz, DMSO-d_6): δ 0.62–0.65 (m, 2H, cyclopentyl $-CH_2$), 0.88–0.94 (m, 2H, cyclopentyl $-CH_2$), 1.81–1.99 (m, 3H, cyclopentyl $-CH_2$ and –

Table 5
Pharmacokinetic parameters for **6f**.

Dose	C_{max}(ng/ml)	C_{max}(uM)	$T_{1/2}$ (h)	AUC_{last}	Co(ng/mL)	Cl(mL/h/kg)	Vd(mL/kg)	% F
PO(10 mg/kg)	153.0	0.45	0.87	315.2	–	–	–	11.3
IV(2 mg/kg)	945.1	2.8	0.85	561.0	1054	3548	4367	

cyclopropyl −*CH*), 2.62 (dd, 4H, J = 7.5 Hz and 15 Hz, cyclopentyl −CH_2), 2.72 (brs, 4H, piperazine −CH_2), 3.58 (s, 4H, piperazine −CH_2), 6.18 (s, 1H, pyrazole −*H*), 8.76 (s, 1H, pyrazole −*NH*), 11.93 (s, 1H, pyrimidine −*NH*). HRMS calcd. for $C_{17}H_{24}N_7[M+H]^+$: 326.2088; found 326.2070; HPLC Retention time – 0.94 min, Purity – 95.42%.

*5.2.3.3. N-(5-cyclopropyl-1H-pyrazol-3-yl)-6,7-dihydro-2-(piperidin-1-yl)-5h-cyclopenta[d]pyrimidin-4-amine (**6c**).* White Solid: Yield 92%, mp 202.2–203.1 °C. ^{1}H NMR (500 Hz, DMSO-d^6): δ 0.62 (d, 2H, J = 3 Hz, cyclopropyl–CH_2), 0.92 (d, 2H, J = 6 Hz, cyclopropyl–CH_2), 1.49 (brs, 4H, piperidine −CH_2), 1.61 (brs, 2H, piperidine–CH_2), 1.86 (m, 1H, cyclopropyl–*CH*), 1.93 (t, 2H, J = 7 Hz, cyclopentyl–CH_2), 2.64 (t, 4H, J = 7 Hz, cyclopentyl–CH_2), 3.66 (brs, 4H, piperidine–CH_2), 6.22 (s, 1H, -pyrazole–*H*), 8.95 (s, 1H, pyrazole–N*H*), 12.02 (s, 1H, pyimidine–N*H*). HRMS calcd. for $C_{18}H_{25}N_6$ $[M+H]^+$: 325.2135; found 325.2112; HPLC Retention time – 3.52 min, Purity – 99.81%.

*5.2.3.4. (1-(4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)-6,7-dihydro-5h-cyclopenta[d]pyrimidin-2-yl)piperidin-3-yl)methanol (**6d**).* Brown Solid: Yield 22%, mp 190–191 °C. Yield: 22%. ^{1}H NMR (300 Hz, DMSO-d^6): δ 0.65–0.66 (d, 2H, J = 3.3 Hz, cyclopropyl–CH_2), 0.88–0.90 (d, 2H, J = 6.3 Hz, cyclopropyl–CH_2), 1.14–1.23 (m, 2H, piperidine–CH_2),1.34–1.38 (m, 1H, piperidine–C*H*), 1.54–1.65 (2H, m, cyclopentyl–CH_2), 1.72–1.90 (m, 4H, pipeidine–CH_2), 2.60 (t, 4H, cyclopentyl–CH_2), 2.80 (m, 1H, cyclopropyl–C*H*), 4.42–4.58 (m, 3*H*, carbinol–CH_2 and – carbinol – O*H* merged), 6.25 (s, 1H, pyrazole–*H*), 8.71 (s, 1H, pyrazole–N*H*), 11.89 (brs, 1H, pyrimidine–N*H*). HRMS calcd. for $C_{19}H_{27}N_6$ $[M+H]^+$: 355.2241; found 355.2236; HPLC Retention time – 2.22 min, Purity – 96.66%.

*5.2.3.5. 1-(4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-yl)-N,N-diethylpiperidine-3-carboxamide (**6e**).* Off White Solid: Yield 22%, mp 194.1–195.0 °C. Yield: 29%. ^{1}H NMR (500 Hz, DMSO-d^6): δ 0.59 (brs, 2H, cyclopropyl–CH_2), 0.89 (d, 2H, J = 7.0 Hz, cyclopropyl–CH_2), 1.00–1.02 (t, 6H, J = 7.00 Hz, ethyl–CH_2),1.41–1.44 (m, 1H, -cyclopropyl–C*H*), 1.58–1.91 (m, 4H, piperidine–CH_2),1.92–1.95 (m, 2H, cyclopentyl–CH_2), 2.54–2.74 (m, 5H, cyclopentyl–CH_2 and - piperidine–CH), 2.77–2.86 (m, 2H, piperidine-CH_2), 3.19–3.34 (m, 4H, ethyl–CH_2), 4.54–4.58 (m, 2H, piperidine–CH_2), 6.15 (brs, 1H, pyrazole–*H*), 8.77 (brs, 1H, pyrazole–N*H*), 11.95 (s, 1H, pyrimidine–N*H*). HRMS calcd. for $C_{23}H_{34}N_7O_1$ $[M+H]^+$: 424.2819; found 424.2840; HPLC Retention time – 3.14 min, Purity – 96.46%.

*5.2.3.6. N-(5-cyclopropyl-1H-pyrazol-3-yl)-6,7-dihydro-2-(4-methylpiperidin-1-yl)-5h-cyclopenta[d]pyrimidin-4-amine (**6f**).* Off White Solid: Yield 82%, mp 188–189 °C. White Solid: Yield 92%, mp 202.2–203.1 ^{0}c. Yield: 42%. ^{1}H NMR (500 Hz, DMSO-d^6): δ 0.63 (d, 2H, J = 5.5 Hz, cyclopropyl–CH_2), 0.90–0.93 (m, 5H, piperidine – CH_3 and – cyclopopyl–CH_2), 0.99–1.06 (m, 2H, piperidine–CH_2), 1.60–1.62 (m, 3H, piperidine–CH_2 and – piperidine–C*H*), 1.84–1.86 (m, 1H, cyclopropyl–C*H*), 1.87–1.95 (m, 2H, cyclopentyl–CH_2), 2.62 (dd, 4H, J = 7.5 Hz and 16.5 Hz, cyclopentyl–CH_2), 2.78 (t, 2H, J = 12.5 Hz–, piperidine–CH_2), 4.53 (d, 2H, J = 12.5 Hz, piperidine–CH_2), 6.21 (brs, 1H, pyrazole–*H*), 8.24 (brs, 1H, pyrazole–N*H*), 11.97 (brs, 1H, pyrimidine–N*H*). HRMS calcd. for $C_{19}H_{27}N_6$ $[M+H]^+$: 339.2292; found 339.2265; HPLC Retention time – 4.48 min, Purity – 99.46.

*5.2.3.7. N-(5-cyclopropyl-1H-pyrazol-3-yl)-6,7-dihydro-2-(4,4-dimethylpiperidin-1-yl)-5h-cyclopenta[d]pyrimidin-4-amine (**6g**).* Brown Solid: Yield 59%, mp 202.2–203.1 °C. ^{1}H NMR (300 Hz, DMSO-d^6): δ 0.60–0.61 (m, 2H, cyclopropyl–CH_2), 0.74–0.96 (m, cyclopropyl–CH_2), 0.86–0.95 (m, 4H, piperidine–CH_2), 1.16 (s, 3H, -methylpiperidine-CH_3), 1.26 ((s, 3H, methylpiperidine–CH_3), 1.28 (s, 1H, methylpiperidine–CH_3), 0.128 (m, 1H, cyclopropyl–C*H*), 1.85 (m, 2H, cyclopentyl–CH_2), 2.57–2.62 (m, 4H, cyclopentyl–CH_2), 3.66 (m, 4H, piperidine–CH_2), 6.19 (s, 1H, pyrazole–*H*), 8.74 (s, 1H, pyrazole–N*H*), 11.93 (s, 1H, pyrimidine–N*H*). HRMS calcd. for $C_{20}H_{29}N_6$ $[M+H]^+$: 353.2448; found 353.2431; HPLC Retention time – 4.88 min, Purity – 98.71.

*5.2.3.8. Ethyl 1-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)-6,7-dihydro-5H-yclopenta[d]pyrimidin-2-yl)piperidine-4-carboxylate (**6h**).* Brown Solid: Yield 65%, mp 210–212 °C. ^{1}H NMR (500 Hz, DMSO-d^6): δ 0.23 (m, 2H, cyclopropyl–CH_2), 0.92 (d, 2H, J = 7 Hz, cyclopropyl–CH_2), 1.83 (t, 3H, J = 7.5 Hz, ethyl - CH_2), 1.44–1.51 (m, 2H, cyclopentyl–CH_2), 1.81–1.95 (m, 5H, piperidine –CH_2 and - cycloypropyl–C*H*), 2.58–2.65 (m, 5H, cyclopentyl–CH_2 and piperidine–C*H*), 2.95 (t, 2H, J = 11.5 Hz, pipeidine–CH_2), 4.07 (dd, 2H, J = 7.0 Hz and 14.0 Hz – ethyl–CH_2), 4.45 (d, 2H, J = 13 Hz, piperidine–CH_2), 6.22 (s, 1H, pyrazole–H), 8.78 (s, 1H, pyrazole–N*H*), 11.97 (s, 1H, pyrimidine–N*H*). HRMS calcd. for $C_{20}H_{29}N_6$ $[M+H]^+$: 397.2347; found 397.2324; HPLC Retention time – 4.64 min, Purity – 98.76%.

*5.2.3.9. 1-(4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-yl)piperidine-4-carbonitrile (**6i**).* White Solid: Yield 92%, mp 202.2– -203.1 °C. ^{1}H NMR (500 Hz, DMSO-d^6): δ 0.63 (d, 2H, J = 4.5 Hz, cyclopropyl–CH_2), 0.92 (d, 2H, J = 6.5 Hz, cyclopropyl–CH_2), 1.63–1.69 (m, 2H, piperdine–CH_2), 1.86–1.94 (m, 5H, piperidine–CH_2 and – cyclopropyl – C*H* and – cyclopentyl–CH_2), 2.63 (dd, 4H, J = 8 Hz and 16 Hz, cyclopentyl–CH_2), 3.09–3.12 (m, 1H, piperidine–C*H*), 3.45–3.49 (m, 2H, piperidine–C*H*), 3.96–3.99 (m, 2H, piperidine–CH_2), 6.20 (s, 1H, Ar–H), 8.80 (s, 1H, pyrazole-N*H*), 11.97 (s, 1H, pyrimidine–N*H*). HRMS calcd. for $C_{19}H_{24}N_7$ $[M+H]^+$: 350.2088; found 350.2067; HPLC Retention time – 3.15 min, Purity – 99.83%; HPLC Retention time – 3.15 min, Purity – 99.83%.

*5.2.3.10. 1-(4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-yl)piperidine-4-carboxylic acid (**6j**).* White Solid: Yield 54%, mp 265.1–267 °C. ^{1}H NMR (300 Hz, DMSO-d_6): δ 0.60–0.65 (m, 2H, cyclopropyl–CH_2), 0.89–0.95 (m, 2H, cyclopropyl–CH_2), 1.44–1.51 (m, 2H, cyclopentyl–CH_2), 1.79–1.94 (m, 5H, piperidine–CH_2 and - cyclopentyl - C*H*), 2.62 (dd, 4H, J = 6.6 Hz and 13.8 Hz - piperidine–CH_2), 2.95 (t, 2H, J = 11.4 Hz, cyclopentyl–CH_2), 4.43 (d, 2H, J = 13.2 Hz, piperidine–CH_2), 6.19 (s, 1H, pyrazole–H), 8.77 (s, 1H, pyrazole–N*H*), 12.04 (brs, 2H, acid-*H* and – pyrimidine–N*H*). HRMS calcd. for $C_{19}H_{25}N_6O_2$ $[M+H]^+$: 369.2034; found 369.2015; HPLC Retention time – 1.13 min, Purity – 98.48%.

*5.2.3.11. 2-(azepan-1-yl)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (**6k**).* Off white Solid: Yield 67%, mp 187–188 °C. ^{1}H NMR (500 Hz, DMSO-d^6): δ 0.61–0.62 (m, 2H, cyclopropyl–C*H*$_2$), 0.92 (brs, 2H, cyclopropyl–C*H*$_2$), 1.47 (brs, 4H, azepane–C*H*$_2$), 1.70 (brs, 4H, azepane–C*H*$_2$), 1.83–1.92 (m, 3H, cyclopentyl–C*H*$_2$ and – cyclopropyl–C*H*), 2.59–2.66 (m, 4H, cyclopentyl–C*H*$_2$), 3.66 (t, 2H, J = 6 Hz, azepane–C*H*$_2$), 6.35 (brs, 1H, pyrazole–*H*), 8.67 (brs, 1H, -pyrazole–N*H*), 11.95 (s, 1H, pyrimidine–N*H*). HRMS calcd for $C_{19}H_{27}N_6$ [M+H] $^{+:}$ 339.2292; found 339.2272; HPLC Retention time – 4.84 min, Purity – 99.52%.

*5.2.3.12. 2-(azocan-1-yl)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (**6l**).* White Solid: Yield 53%, mp 230–232 °C. ^{1}H NMR (500 Hz, DMSO-d^6): δ 0.60–0.61 (m, 2H, cyclopropyl–C*H*$_2$), 0.93 (brs, 2H, cyclopropyl–C*H*$_2$), 1.43 (brs, 2H, azocane–C*H*$_2$), 1.49 (brs, 4H, azocane–C*H*$_2$), 1.71 (brs, 4H, azocane–C*H*$_2$), 1.91–1.92 (m, 3H, cyclopropyl–C*H* and – cyclopentyl–C*H*$_2$), 2.59–2.66 (m, 4H, cyclopentyl–C*H*$_2$), 3.63 (t, 4H, J = 5.5 Hz, azocane–C*H*$_2$), 6.35 (brs, 1H, pyrazole–*H*), 8.65 (brs, 1H, pyraole –N*H*), 11.96 (brs, 1H, pyrimidine –C*H*$_2$). HRMS calcd. for $C_{20}H_{29}N_6$ [M+H]$^+$: 353.2448, found 353.2480; HPLC Retention time – 5.71 min, Purity – 99.21%.

*5.2.3.13. 2-(2-aza-bicyclo[2.2.1]heptan-2-yl)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (**6m**).* White Solid: Yield 17%, mp 189–191 °C. ^{1}H NMR (300 Hz, DMSO-d^6): δ 0.76 (brs, 2H, cyclopropyl–C*H*$_2$), 0.89 (brs, 2H, cyclopropyl–C*H*$_2$), 1.26–2.13 (m, 13H, cyclopentyl and -azabicycloheptan –C*H*$_2$), 2.68–2.78 (m, 2H, cyclopentyl–C*H*$_2$), 3.04–3.24 (m, 1H, azabicycloheptan –C*H*), 4.06 (brs, 1H, azabicycloheptan –C*H*), 6.33 (brs, 1H, Ar–H), 9.12 (brs, 1H, pyrazole-N*H*). ESI-MS *m/z*: 337.3; HPLC Retention time – 2.73 min, Purity – 98.08%.

*5.2.3.14. N2-benzyl-N4- 20 -(5-cyclopropyl-1H-pyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (**6n**).* White Solid: Yield 45%, mp 200–201 °C. ^{1}H NMR (300 Hz, DMSO-d$_6$): δ 0.56 (brs, 2H, cyclopropyl-C*H*$_2$), 0.83 (d, 2H, J = 6.3 Hz, cyclopropyl–C*H*$_2$), 1.77–1.79 (m, 1H, cyclopropyl–C*H*), 1.92–1.94 (m, 1H cyclopentyl–C*H*$_2$), 2.62 (dd, 4H, J = 7.2 Hz and 14.7 Hz, cyclopentyl–C*H*$_2$), 3.71 (s, 1H, benzylamine-N*H*), 4.48 (d, 2H, J = 6.3 Hz, benzyl–C*H*$_2$), 6.26 (brs, 1H, Ar–*H*), 7.21–7.31 (m, 5H, Ar–*H*), 8.67 (brs, 1H, pyrazole-N*H*), 11.85 (brs, 1H, pyrimidine-N*H*). HRMS calcd for $C_{20}H_{23}N_6$ [M+H]$^+$: 347.1979; found 347.1952 HPLC Retention time – 3.12 min, Purity – 98.53%.

*5.2.3.15. N4-5-cyclopropyl-1H-pyrazol-3-yl)-N2-(4-methylbenzyl)-6,7-dihydro-5h-cyclopenta[d]pyrimidine-2,4-diamine (**6o**).* White Solid: Yield 57%, mp 180–182 °C. ^{1}H NMR (300 Hz, DMSO-d$_6$): δ 0.57 (brs, 2H, cyclopentyl–C*H*$_2$), 0.83–0.85 (m, 2H, cyclopentyl–C*H*$_2$), 1.75–1.81 (m, 1H, cyclopropyl–C*H*), 1.91–1.94 (m, 2H, cyclopentyl–C*H*$_2$), 2.26 (s, 3H, benzyl–C*H*$_2$), 2.57–2.66 (m, 4H, cyclopentyl–C*H*$_2$), 4.43 (d, 2H, J = 5.7 Hz, benzyl–C*H*$_2$), 6.19 (brs, 1H, pyrazole -*H*), 7.10 (d, 2H, J = 6.00 Hz, pyrazole -*H*), 7.19 (d, 2H, J = 6.9 Hz, Ar–*H*), 8.77 (brs, 1H, pyrazole-N*H*), 9.32 (brs, 1H, pyrimidine-N*H*), 11.99 (brs, 1H, pyrimidine–N*H*). HRMS calcd. for $C_{21}H_{25}N_6$ [M+H]$^+$: 361.2135; found 361.2112; HPLC Retention time – 4.13 min, Purity - 97.25%.

*5.2.3.16. 2-(4-Methylpiperidin-1-yl)-N-(5-phenyl-1H-pyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (**7a**).* Off White Solid: Yield 62%, mp 246–247 °C. ^{1}H NMR (300 Hz, DMSO-d$_6$): δ 0.88 (d, 3H, J = 6 Hz, piperidine –C*H*$_3$), 1.01–1.20 (m, 2H, piperidine–C*H*$_2$), 1.59–1.63 (m, 3H, piperidine–C*H*$_2$),1.88–1.93 (m, 2H, piperidine–C*H*$_2$), 2.58–2.68 (m, 4H, cyclopentyl–C*H*$_2$), 2.79 (t, 2H, J = 12.3 Hz, cyclopentyl–C*H*$_2$),4.59 (d, 2H, J = 13.2 Hz, piperidine –C*H*$_2$), 6.98 (d, 2H, J = 1.5 Hz, pyrazole–*H*), 7.29–7.324 (m, 1H, Ar–*H*), 7.44 (t, 2H, J = 7.5 Hz, Ar–*H*), 7.64 (d, 2H, J = 7.5 Hz, Ar–H), 8.92 (s, 1H, pyrazole–N*H*), 12.72 (s, 1H, pyrimidine–N*H*). HRMS calcd. for $C_{22}H_{27}N_6$ [M+H]$^+$: 375.2292; found 375.2244 HPLC Retention time – 5.96 min, Purity – 99.50%.

*5.2.3.17. 2-(azepan-1-yl)-N-(5-phenyl-1H-pyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (**7b**).* Off White Solid: Yield 46%, mp 238–239 °C. ^{1}H NMR (300 Hz, DMSO-d$_6$): δ 1.46 (bs, 4H, azepane–C*H*$_2$), 1.72 (bs, 4H, azepane –C*H*$_2$),1.90–1.93 (m, 2H, cyclopentyl–C*H*$_2$), 2.60–2.69 (m, 4H, cyclopentyl –C*H*$_2$), 3.69 (bs, 4H, azepane–C*H*$_2$), 7.09 (s, 1H, Ar–*H*), 7.30–7.43 (m, 3H, Ar–*H*), 7.62–7.65 (m, 2H, Ar–*H*), 8.7 (s, 1H, pyrazole–N*H*), 12.69 (s, 1H, pyrimidine–N*H*). HRMS calcd. for $C_{22}H_{27}N_6$ [M+H]$^+$: 375.2292; found 375.2244; HPLC Retention time – 5.54 min, Purity – 95.87%.

*5.2.4. Procedure for the synthesis of compound **8***

Compound 4 (0.100 g, 0.363 mmol), phenyl boronic acid (0.053 g, 0.435 mmol), tetrakis(triphenylphosphine)palladium(0) (0.021 g, 0.018 mmol) and Na_2CO_3 (0.075 gm, 0.544 mmol) were dissolved in DME (5 mL) and water (1 mL) in a 10 mL microwave reactor. The reactor was flushed with argon, and heated at 180° C for 55 min. Then reaction mass was diluted with water (10 mL) and washed with EtOAc (3 × 5 mL). The combined organics were washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified using by silica gel column chromatography using CH_2Cl_2/MeOH (100/1) as eluent to obtain the solid compounds as desired product.

*5.2.4.1. N-(5-cyclopropyl-1H-pyrazol-3-yl)-6,7-dihydro-2-phenyl-5h- cyclopenta[d]pyrimidin-4-amine (**8**).* Off White Solid: Yield 53%, mp 194–196 °C. ^{1}H NMR (300 Hz, $CDCl_3$): δ 0.63–0.75 (m, 2H, cyclopentyl –C*H*$_2$), 0.98–1.02 (m, 2H, cyclopentyl–C*H*$_2$), 1.89–1.98 (m, 1H, cyclopropyl–C*H*), 2.16–2.26 (m, 2H, cyclopentyl–C*H*$_2$), 2.83 (t, J = 7.2 Hz, cyclopentyl–C*H*$_2$), 3.05 (t, 2H, J = 7.2 Hz, cyclopentyl–C*H*$_2$), 6.40 (s, 1H, pyrazole -*H*), 6.98 (brs, 1H, pyrazole–N*H*), 7.43–7.57 (m, 4H, Ar–*H*), 7.65–7.72 (m, 1H, Ar–*H*). HRMS calcd. for C19H20N5 [M+H]$^+$: 318.1713, found 318.1688; HPLC Retention time – 4.31 min, Purity – 95.41%.

*5.2.5. General procedure for the synthesis of compound **14a–d**, **15a–d** and **36–39***

Appropriate amines (0.399 mmol) and triethyl amine (0.253 ml, 1.813 mmol) were added to a stirred solution of **12/13/32–35** (0.363 mmol) in NMP (5 mL) in a 10 mL microwave reactor. The reactor was flushed with argon, and heated at 160° C for 20 min. The reaction mass was diluted with water (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using CH_2Cl_2/MeOH 100/1 to 100/10) as eluent to obtain desired compounds.

*5.2.5.1. 6,7-Dihydro-N-(5-methyl-1H-pyrazol-3-yl)-2-(piperidin-1-yl)-5H-cyclopenta[d]pyrimidin-4-amine (**14a**).* Off White Solid: Yield 59%, mp 220–221.3 °C. ^{1}H NMR (300 Hz, DMSO-d^6): δ 1.47 (brs, 4H, piperidine–C*H*$_2$), 1.58 (brs, 2H, piperidine–C*H*$_2$), 1.91–1.98 (m, 2H, cyclopentyl–C*H*$_2$), 2.19 (s, 3H, pyrazole methyl-C*H*$_3$), 2.57–2.63 (m, 4H, cyclopentyl–C*H*$_2$), 3.65 (brs, 4H, piperidine–C*H*$_2$), 6.33 (s, 1H, pyrazole–*H*), 8.65 (s, 1H, pyrazole–N*H*), 11.87 (s, 1H, pyrimidine–N*H*). HRMS calcd for $C_{16}H_{23}N_6$ [M+H] $^+$: 299.1979; found 299.1959; HPLC Retention time – 2.78 min, Purity – 98.76%.

*5.2.5.2. 6, 7-Dihydro-N-(5-methyl-1H-pyrazol-3-yl)-2-(4-methylpiperidin-1-yl)-5H-cyclopenta[d]pyrimidin-4-amine (**14b**).* Grey Solid: Yield 58%, mp 226–228 °C. ^{1}H NMR (300 Hz, DMSO-d^6): δ 0.89–1.03 (m, 5H, piperdine–C*H*$_2$), and –pipeidine–C*H*$_2$), 1.61 (d, 2H, J = 10.8 Hz, -methylpiperidine- C*H*$_2$)), 1.91 (brs, 2H, cyclopentyl–C*H*$_2$), 2.60–2.63 (m, 4H, cyclopentyl–C*H*$_2$), 2.76 (t, 2H, J = 12.5 Hz, -methylpiperidine–C*H*$_2$), 4.56 (d, 2H, J = 12.3 Hz, methylpiperidine–C*H*$_2$), 6.32 (s, 1H, pyrazole -*H*), 8.66 (s, 1H, pyrazole-N*H*), 11.86 (s, 1H, pyrimidine–N*H*). HRMS calcd for $C_{17}H_{25}N_6$ [M+H] $^+$: 313.2135, found 313.2112; HPLC Retention time – 3.45 min, Purity – 99.23%.

*5.2.5.3. 2-(azepan-1-yl)-6,7-dihydro-N-(5-methyl-1H-pyrazol-3-yl)-5H-cyclopenta[d]pyrimidin-4-amine (**14c**).* Off White Solid: Yield 35%, mp 233–234 °C. ^{1}H NMR (300 Hz, DMSO-d^6): δ 1.46 (brs, 4H, azepane–C*H*$_2$), 1.70 (brs, 4H, azepane–C*H*$_2$), 1.90–1.92 (m, 2H, cyclopentyl–C*H*$_2$), 2.19 (s, methylpyrazole–C*H*$_3$), 2.57–2.66 (m, 4H, cyclopentyl–C*H*$_2$), 3.66 (t, 4H, J = 5.4 Hz, -azepane–C*H*$_2$), 6.44 (s, 1H, pyrazole–*H*), 8.60 (s, 1H, pyrazole–N*H*), 11.84 (s, 1H, pyrimidine–N*H*). HPLC Retention time – 4.31 min, Purity – 95.41%.

*5.2.5.4. Ethyl 1-(4-(5-methyl-1H-pyrazol-3-ylamino)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-yl)piperidine-3-carboxylate (**14d**).* Brown Solid: Yield 62%, mp 238–239 °C. ^{1}H NMR (300 Hz, DMSO-d^6): δ Yield = 35%. ^{1}H NMR (300 Hz, DMSO-d^6): δ 1.46 (brs, 4H, azepane–C*H*$_2$), 1.70 (brs, 4H, azepane–C*H*$_2$), 1.90– -1.92 (m, 2H, cyclopentyl–C*H*$_2$), 2.19 (s, methylpyrazole–C*H*$_3$), 2.57–2.66 (m, 4H, cyclopentyl–C*H*$_2$), 3.66 (t, 4H, J = 5.4 Hz, -azepane–C*H*$_2$), 6.44 (s, 1H, pyrazole–*H*), 8.60 (s, 1H, pyrazole–N*H*), 11.84 (s, 1H, pyrimidine–N*H*). HRMS calcd for $C_{19}H_{27}N_6$ O_2[M+H]$^+$: 371.2190, found 371.2173 5516–02; HPLC Retention time – 3.58 min, Purity - 95.41%.

*5.2.5.5. N-(5-tert-butyl-1H-pyrazol-3-yl)-6,7-dihydro-2-(piperidin-1-yl)-5h-cyclopenta[d]pyrimidin-4-amine (**15a**).* White Solid: Yield 59%, mp 237–239.3 °C. ^{1}H NMR (300 Hz, DMSO-d^6): δ 1.26 (s, 9H, t-butyl –C*H*$_3$),1.47 (bs, 4H, piperidine–C*H*$_2$), 1.60–1.61 (m, 2H, piperidine–C*H*$_2$), 1.90–1.93 (m, 2H, cyclopentyl–*H*$_2$), 2.59–2.66 (m, 4H, cyclopentyl–C*H*$_2$), 3.67–3.69 (m, 4H, piperidine–C*H*$_2$), 6.55 (s, 1H, pyrazole–*H*), 8.76 (s, 1H, pyrazole–N*H*), 11.91 (s, 1H, pyrimidine–N*H*). HRMS calcd. for $C_{19}H_{27}N_6$ O_2[M+H]$^+$: 341.2448; found 341.2415; HPLC Retention time – 4.38 min, Purity – 99.23%.

*5.2.5.6. N-(5-tert-butyl-1H-pyrazol-3-yl)-6,7-dihydro-2-(4-methylpiperidin-1-yl)-5h-cyclopenta[d]pyrimidin-4-amine (**15b**).* Off White Solid: Yield 82%, mp 241–242.2 °C. ^{1}H NMR (500 Hz, DMSO): δ 0.89–0.91 (d, 2H, J = 6 Hz, piperidine–C*H*$_3$), 0.102–0.04 (m, 2H, piperidine – C*H*$_2$), 1.26 (s, 9H, t-Butyl –C*H*$_3$), 1.60 (d, 3H, piperidine – CH and – piperidine–C*H*$_2$), 1.90–1.93 (m, 2H, cyclopentyl –C*H*$_2$), 2.59–2.66 (m, 4H, cyclopentyl–C*H*$_2$), 2.78 (t, 2H, J = 12 Hz, piperidine – C*H*$_2$), 5.58 (d, 2H, J = 13 Hz, piperidine – C*H*$_2$), 6.44 (s, 1H, pyrazole–*H*), 8.77 (s, 1H, pyrazole–N*H*), 11.91 (s, 1H, Pyrimidine-N*H*). HRMS calcd for $C_{20}H_{31}N_6$ [M+H] $^+$: 355.2605, found 355.2606; HPLC Retention time – 4.31 min, Purity – 98.61%.

*5.2.5.7. N-(5-tert-butyl-1H-pyrazol-3-yl)-2-(azepan-1-yl)-6,7-dihydro-5h-cyclopenta[d]pyrimidin-4-amine (**15c**).* Brown Solid: Yield 62%, mp 246–247 °C. ^{1}H NMR (300 Hz, CDCl$_3$): δ 1.27 (brs, 4H, -azepane-C*H*$_2$), 1.35 (s, 9H, t-butylpyrazole-C*H*$_3$), 1.84 (brs, 4H, azepane–C*H*$_2$), 2.06–2.11 (m, 2H, cyclopentyl–C*H*$_2$), 2.67 (t, 2H, J = 6.6 Hz, cyclopentyl–CH2), 2.81 (t, 2H, J = 7.5 Hz, cyclopentyl–C*H*$_2$), 3.78 (t, 4H, J = 5.4 Hz, azepane–C*H*$_2$), 6.38 (s, 1H, pyrazole -*H*), 6.62 (s, 1H, pyrazole–NH). HRMS calcd. for $C_{16}H_{31}N_6O_3$ [M+H]$^+$: 355.2452; found 355.2487; HPLC Retention time – 4.29 min, Purity – 97.76%.

*5.2.5.8. Ethyl 1-(4-(5-tert-butyl-1H-pyrazol-3-ylamino)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-yl)piperidine-3-carboxylate (**15d**).* Off white Solid: Yield 65%, mp 251–252 °C. ^{1}H NMR (300 Hz, CDCl$_3$): δ 1.26 (t, 3H, J = 6.9 Hz. – ethyl–C*H*$_2$), 1.35 (s, 9H, t-butyl –C*H*$_3$), 1.56–1.69 (m, 2H, piperidine–C*H*$_2$), 1.73–1.83 (m, 2H, piperidine –C*H*$_2$), 2.04–2.12 (m, 2H, cyclopentyl–C*H*$_2$), 2.54–2.60 (m, 1H, piperidine–CH), 2.64–2.69 (m, 2H, cyclopentyl–C*H*$_2$), 2.78–2.86 (m, 2H, cyclopentyl-C*H*$_2$), 3.02–3.10 (m, 1H, piperidine–C*H*$_2$), 3.21–3.28 (m, 1H, piperidine–C*H*$_2$), 4.15 (q, 2H, J = , ethyl–C*H*$_2$), 4.50 (d, 1H, J = 12.9 Hz, piperidine-C*H*$_2$), 4.75 (d, 1H, J = 11.4 Hz, piperidine–C*H*$_2$), 6.44 (brs, 1H, pyrazole–*H*), 6.65 (s, 1H, pyrazole–N*H*). HRMS calcd. for $C_{22}H_{33}N_6O_2$ [M+H]$^+$: 413.2660; found 413.2657; HPLC Retention time – 5.06 min, Purity – 98.92%.

*5.2.5.9. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-(4-methylpiperidin-1-yl)-5,6,7,8-tetrahydro-5,8-methanoquinazolin-4-amine (**36**).* Brown Solid: Yield 74%, mp 237.1–238 °C. ^{1}H NMR (300 Hz, CDCl$_3$): δ 0.75 (brs, 2H, cyclopentyl–C*H*$_2$), 0.97–0.99 (5H, m, piperidine–C*H*$_3$ and – cycloropyl–C*H*$_2$), 1.20–1.27 (m, 4H, piperidine–C*H*$_2$), 1.49 (m, 1H, piperidine–C*H*), 1.72–1.75 (m, 4H, camphor–C*H*$_2$), 1.91 (m, 3H, -piperdine - CH and – camphor–C*H*$_2$), 2.89 (t, 2H, J = 12.3 Hz, camphor–C*H*), 3.23 (d, 2H, J = 17.1 Hz, piperidine–C*H*), 4.62 (d, J = 12.0 Hz, piperidine–C*H*), 5.94 (s, 1H, pyrazole–N*H*), 6.21 (s, 1H, pyrazole–*H*). HRMS calcd for $C_{21}H_{29}N_6$ [M+H]$^+$: 365.2448, found 365.2443; HPLC Retention time – 5.43 min, Purity – 99.59%.

*5.2.5.10. N-(5-cyclopropyl-1H-pyrazol-3-yl)-7,7-difluoro-6,7-dihydro-2-(4-methylpiperidin-1-yl)-5h-cyclopenta[d]pyrimidin-4-amine (**37**).* Yellow Solid: Yield 79%, mp 225–226.1 °C. ^{1}H NMR (300 Hz, DMSO-d^6): δ 0.65 (brs, 2H, cyclopopyl-C*H*$_2$), 0.91–0.96 (m, 5H, piperidine–CH$_3$ and – cyclopropyl–C*H*$_2$), 1.02–1.06 (m, 2H, piperidine–C*H*$_2$), 1.34 (brs, 1H, piperidine–C*H*), 1.63–1.66 (m, 2H, piperidine–C*H*$_2$), 1.88–1.91 (m, 1H, cyclopropyl–C*H*), 2.70–2.73 (m, 3H, cyclopropyl–C*H*$_2$ and – piperidine–C*H*$_2$), 2.80–2.89 (m, 3H, cyclopropyl –C*H*$_2$ and – piperidine–C*H*$_2$), 4.56 (d, J = 12.3 Hz, piperidine –C*H*$_2$), 6.27 (s, 1H, pyrazole–*H*), 9.43 (s, 1H, pyrazole–N*H*), 12.12 (s, 1H, pyrimidine–N*H*). HRMS calcd for $C_{19}H_{25}F_2N_6$ [M+H]$^+$: 375.2123, found 375.2088; HPLC Retention time – 6.41 min, Purity – 97.37%.

*5.2.5.11. N-(5-cyclopropyl-1H-pyrazol-3-yl)-6,7-dihydro-7,7-dimethyl-2-(4-methylpiperidin-1-yl)-5h-cyclopenta[d]pyrimidin-4-amine (**38**).* Grey Solid: Yield 79%, mp 228–230.1 °C. ^{1}H NMR (300 Hz, CDCl$_3$): δ 0.74–0.76 (m, 2H, cyclopropyl–C*H*$_2$), 0.94–0.98 (m, 5H, cyclopropyl - C*H*$_2$ and – piperidine–C*H*$_3$), 1.20 (s, 6H, cyclopentyl–C*H*$_3$), 1.22–1.27 (m, 2H, piperidine–C*H*$_2$), 1.69–1.73 (m, 3H, piperidine - C*H*$_2$ and – piperidine –C*H*), 1.91–1.95 (m, cyclopentyl –C*H*$_2$ and – cyclopropyl–C*H*), 2.57 (t, 2H, J = 6.9 Hz, cyclopentyl–C*H*$_2$), 2.89 (t, 2H, J = 12 Hz, piperidine–C*H*$_2$), 4.68 (d, 2H, J = 12.9 Hz, piperidine–C*H*$_2$), 5.92 (s, 1H, pyrazole–*H*), 6.50 (s, 1H, pyrazole–N*H*). HRMS calcd. for $C_{21}H_{31}N_6$ [M+H]$^+$: 367.2605; found 367.2611; HPLC Retention time – 7.32 min, Purity – 99.33%.

*5.2.5.12. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-(4-methylpiperidin-1-yl)-5,6-dihydrospiro[cyclopenta[d]pyrimidine-7,1'-cyclopentan]-4-amine (**39**).* White Solid: Yield 32%, mp 235–237. ^{1}H NMR (300 Hz, CDCl$_3$): δ 0.76 (brs, 2H, cyclopentyl–C*H*$_2$), 0.96 (s, 3H, piperidine–C*H*$_3$), 0.98 (brs, 2H, cyclopropyl–C*H*$_2$), 1.58–1.73 (m, 7H, cyclopentyl -C*H*$_2$ and - piperidine–C*H*), 1.90–2.00 (m, 7H, cyclopentyl – C*H*$_2$ and – cyclopropyl–C*H*), 2.56 (t, 2H, J = 6.6 Hz, cyclopentyl–C*H*$_2$), 2.88 (t, 2H, J = 12.3 Hz, piperidine–C*H*$_2$), 4.65 (d, 2H, J = 12.6 Hz, piperidine–C*H*$_2$), 5.90 (brs, 1H, pyrazole–*H*), 6.50 (s, 1H, pyrazole–N*H*). HRMS calcd. for $C_{21}H_{31}N_6$ [M+H]$^+$: 393.2761; found 393.2755; HPLC Retention time – 5.94 min, Purity – 95.02%.

5.3. Biological assays

5.3.1. Kinase assay

The *in vitro* kinase assays using IGF-1R and IR kinase proteins (made in house) were conducted using a homogeneous time-resolved fluorescence assay. The standard enzyme reaction buffer consisted of 50 mM Tris HCL (pH: 7.4), 1 mM EGTA, 10 mM $MgCl_2$, 2 mM DTT, 0.01% Tween-20, IGF-1R/IR kinase enzyme, poly GT peptide substrate (Perkin Elmer [Ulight Glu–Tyr (4:1)]n) and ATP [concentration equivalent to Km]. Inhibitors in DMSO were added to give a final inhibitor concentration ranging from 40 μM to 40 pM. Briefly, 25 nM of IGF-1R or 0.5 nM of IR protein was pre incubated with various concentrations of the compound for 10 min at 23 °C followed by the addition of 50 nM of poly GT substrate. Reaction was initiated with the addition of ATP (final concentration of 20 μM for IGF-1R assay and 10 μM for IR assay). After 1 hr incubation at 23 °C, kinase reaction was stopped with the addition of 10 mM EDTA. Europium cryptate – labelled antiphosphotyrosine antibody PY20 (5 μl) was added (final concentration of 2 nM) and the mixture was allowed to equilibrate for 1 h at 23 °C followed by reading the plate in Envision plate reader. The intensity of light emission at 665 nM was directly proportional to the level of substrate phosphorylation. The IC50 values for inhibitors were determined by a four-parameter sigmoidal curve fit (Graph pad prism).

5.3.2. Cell growth inhibition assay

Effect of the IGFR/IR kinase inhibitors on cell proliferation was evaluated on various solid cancer cell lines (all purchased from ATCC) using Propidium Iodide staining method. Briefly, cells were seeded in a 96 well white bottom plate at a density of 3000 cells/well in 100 μl complete medium and incubated at 37 °C in 5% CO_2 incubator. Next day cells were treated with increasing doses of the compound and the plate was further incubated for 48 h at 37 °C in 5% CO_2 incubator. After 48 hrs of compound treatment the medium from the plate was removed and cells were washed with 1X PBS followed by the addition of 200 μl of Propidium Iodide solution made in PBS (7 ug/ml). The plate was frozen overnight at −70 °C. Next day, the plate was thawed and the fluorescence intensity was measured.

5.4. Docking

Molecular Docking Studies: Molecular docking studies were carried out using the three dimensional crystal structure of IGF-1R protein obtained from protein data bank with the PDB code 3I81 co-crystallized with BMS754807. The choice of the protein was based on its good resolution and structural similarity of the co-crystallized ligand to the in-house synthesized compounds. Docking studies were done using GLIDE 6.0 module (ref: GLIDE, version 6.0; Schrödinger, LLC: New York, NY, 2013.) of Schrodinger Suite of programs (2013). The ligands were prepared by LIGPREP module and the protein was prepared, optimized and minimized by Protein Preparation Wizard using OPLS-2005 force field. Active site for docking was defined as a grid box of dimensions 24 × 24 × 24 $Å^3$ around the centroid of the ligand. Docking of molecules was done using Glide XP module with Epik penalties for different ionizations and tautomeric states. Ten docked poses per ligand were generated and analysed.

5.5. Pharmacokinetic studies in rats

Male Sprague Dawley rats (200–300 g) bred in-house at Piramal Enterprises Limited, Goregaon, Mumbai, India were used. Rats were maintained in a temperature of 22°C ± 2 °C and humidity (55% ± 5%) controlled room with a 12 h light/dark cycle and free access to standard diet and water. Animals (n = 3 per study) were fasted overnight before dosing, and food was returned 4 h post-dose; water was provided ad libitum. For oral administration, **6f** was formulated with 0.25% (w/v) methyl cellulose solution in water. For all intravenous routes of administration, **6f** was formulated with 10% (v/v) DMSO, 30% (v/v) PEG 400, 5% (v/v) Tween 80 and 55% water for injection. Rats were fasted overnight (~16 h) with free access to water. **6f** was administered to Sprague Dawley rats at a dose of 2 mg/kg bodyweight, intravenously, and 10 mg/kg orally. Following intravenous administration, blood samples (0.25 mL) were collected at 0.033, 0.083, 0.25, 0.50, 1, 2, 4, 6, 8, 12, 24 and 30 h post-dose. Following oral administration, blood samples (0.25 mL) were collected at 0.083, 0.25, 0.50, 0.75, 1, 2, 4, 6, 8, 10, 12, 24 and 30 h post-dose. Plasma was separated by centrifugation at 10,000,000 rpm for 5 min at 4 °C and plasma samples were stored at approximately −70 °C until bioanalysis by a fit-for-purpose LC-MS/MS method.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.12.053.

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