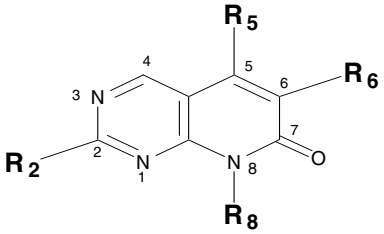
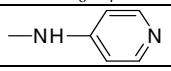
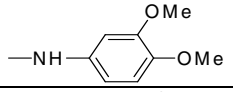
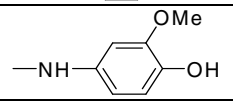
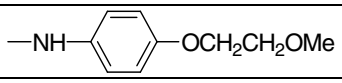
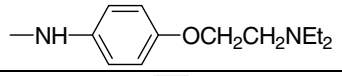
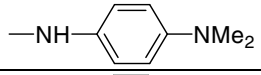
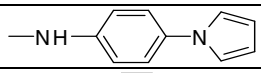
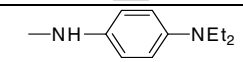
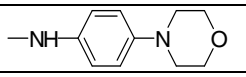
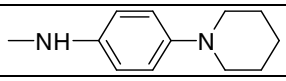
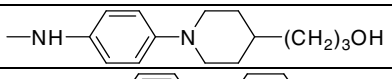
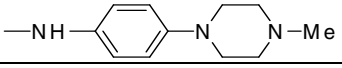
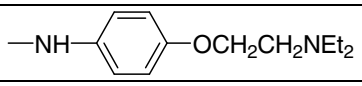
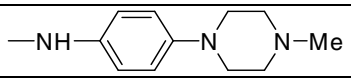
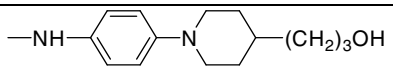
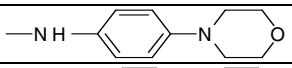
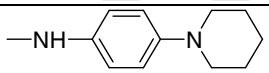
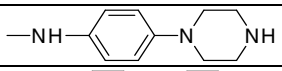
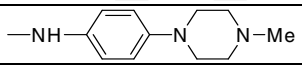
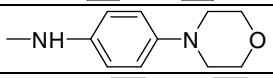
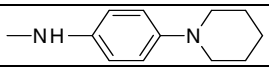
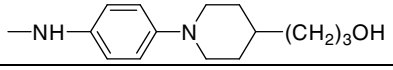
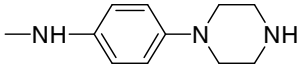
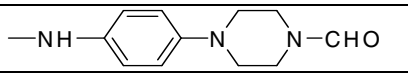
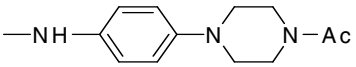
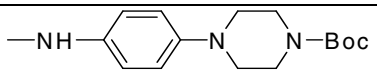
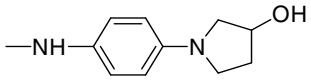
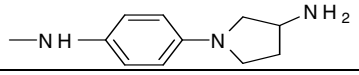
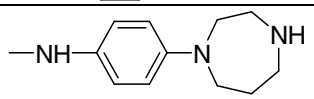
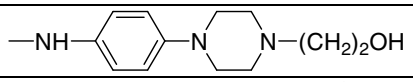
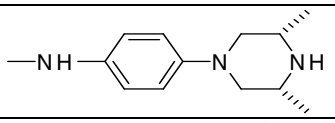
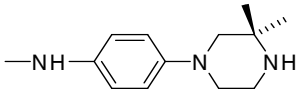
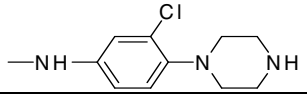
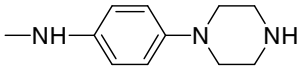
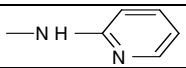
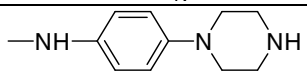
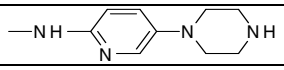
Table 1. Structures selected for the study with their pIC_{50} values



Mol ID	pIC_{50}	R_2	R_5	R_6	R_8
1	6.21	-NHPh	H	H	Et
2	4.92	-NHEt	H	H	"
3	5.36	-NH^{i}Pr	H	H	"
4	5.28	-NH^{t}Bu	H	H	"
5	5.48	-NH-cyclohexyl	H	H	"
6	5.91	-NH-C_6H_4-p-F	H	H	"
7	5.85	-NH-C_6H_4-m-F	H	H	"
8	5.93		H	H	"
9	5.11	-NH-C_6H_4-m-O(CF_2CHF_2)	H	H	"
10	6.22	-NH-C_6H_4-p-Me	H	H	"
11	6.23	-NH-C_6H_4-OH	H	H	"
12	5.39		H	H	"
13	5.74		H	H	"
14	5.63		H	H	"
15	6.80		H	H	"
16	6.48		H	H	"
17	5.56		H	H	"
18	5.85		H	H	"
19	6.52		H	H	"
20	6.52		H	H	"
21	6.05		H	H	"
22	7.07		H	H	"
23	5.26	-NHPh	H	H	Me
24	6.84	"	H	H	isopropyl
25	6.26	"	H	H	n-propyl
26	6.72	"	H	H	sec-butyl
27	5.83	"	H	H	isobutyl
28	6.53	"	H	H	n-butyl
29	6.80	"	H	H	isopentyl
30	6.68	"	H	H	cyclopentyl

31	7.33	"	H	H	cyclohexyl
32	6.74	"	H	H	cycloheptyl
33	7.42	"	H	H	exo-1-bicyclo-[2.2.1]hept-2-yl
34	5.78	"	H	H	phenyl
35	4.87	"	H	H	cyclohexylmethyl
36	6.03	"	H	H	benzyl
37	5.38	"	H	H	methoxymethyl
38	5.54	"	H	H	2-methoxyethyl
39	5.11	"	H	H	2-ethoxyethyl
40	5.30	"	H	H	C-oxiranylmethyl
41	4.51	"	H	H	CH_2CO_2Me
42	7.35		H	H	isopropyl
43	8.15	"	H	H	cyclopentyl
44	7.96	"	H	H	cyclohexyl
45	8.40	"	H	H	cycloheptyl
46	6.35	"	H	H	exo-1-bicyclo-[2.2.1]hept-2-yl
47	5.68		H	H	2-benzyloxyethyl
48	5.78	"	H	H	$CH_2(CHOH)CH_2OH$
49	6.76	"	H	H	phenyl
50	6.85	"	H	H	cyclopropyl
51	7.07	"	H	H	isopropyl
52	7.89	"	H	H	isopentyl
53	8.05	"	H	H	cyclopentyl
54	8.22	"	H	H	exo-1-bicyclo-[2.2.1]hept-2-yl
55	8.40	"	H	H	cyclohexyl
56	7.47		H	H	cyclopentyl
57	8.10	"	H	H	exo-1-bicyclo-[2.2.1]hept-2-yl
58	8.00		H	H	Cyclopentyl
59	8.00		H	H	"
60	8.22		H	H	"
61	7.74		Me	H	"
62	6.94		Me	H	"
63	6.74		Me	H	"
64	6.94		Me	H	"
65	7.85		Me	H	"
66	6.18	"	Et	H	"
67	5.58	"	CF_3	H	"
68	6.58	"	Me	H	isopropyl
69	5.97	"	Me	H	isopentyl

70	6.79		Me	H	"
71	6.99		Me	H	"
72	6.37		Me	H	"
73	6.59		Me	H	"
74	7.19		Me	H	"
75	7.28		Me	H	"
76	7.46		Me	H	"
77	6.62		Me	H	"
78	7.19		Me	H	"
79	7.55		Me	H	"
80	6.78		Me	Me	"
81	7.60	"	Me	Et	"
82	7.52	"	Me	F	"
83	7.80	"	Me	Cl	"
84	8.30	"	Me	I	"
85	7.49	"	Me	COOH	"
86	8.40	"	Me	CO_2Me	"
87	6.84		H	H	"
88	8.70		H	Br	"
89	7.80		H	Br	"
90	7.04	"	H	H	cyclopropyl
91	7.82	"	H	H	cyclopentyl
92	7.89	"	H	H	cyclohexyl
93	7.29	"	H	F	cyclopentyl
94	7.72	"	H	NH_2	"
95	7.57	"	H	Me	"
96	7.66	"	H	Et	"
97	7.89	"	H	CH_2OH	"
98	7.89	"	H	CH_2OMe	"
99	7.74	"	H	CH_2OEt	"
100	7.51	"	H	$CH_2O(CH_2)_2OMe$	"
101	6.91	"	"	$(CH_2)_2OEt$	"
102	7.43	"	"	$O(CH_2)_2OEt$	"
103	5.75	"	"	$OCH_2{}^iPr$	"
104	6.91	"	"	Ac	"
105	6.23	"	"	CO_2Et	"

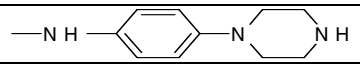
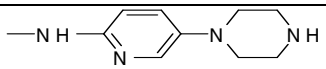
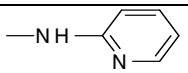
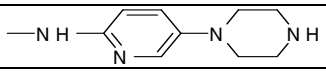
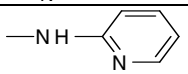
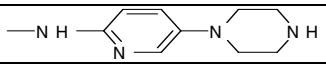
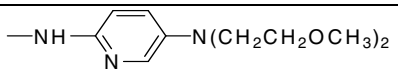
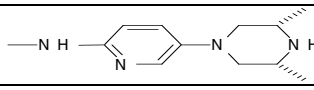
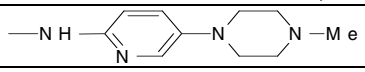
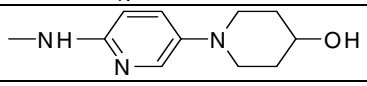
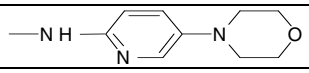
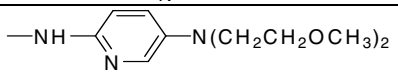
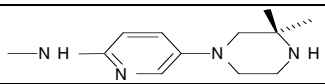
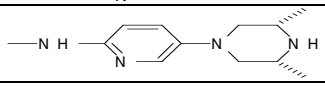
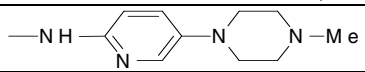
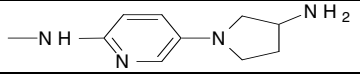
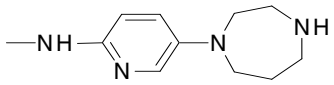
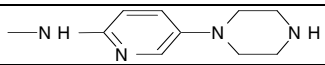
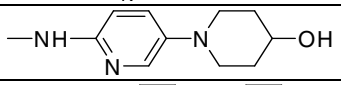
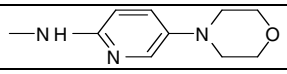
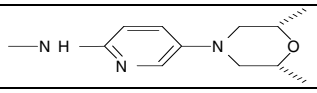
106	8.30		Me	Br	"
107	8.70	"	Me	Ac	"
108	8.22	"	Me	CO_2Et	"
109	6.24		Me	H	"
110	6.02		H	Br	"
111	6.80		Me	Br	"
112	6.36		Me	Ac	"
113	7.96		Me	Ac	"
114	7.31	"	Me	CO_2Et	"
115	5.96		Me	Br	"
116	7.20		Me	Br	"
117	6.87		Me	Br	"
118	7.13		Me	Br	"
119	5.71		Me	Br	"
120	7.29		Me	Ac	"
121	7.68		Me	Ac	"
122	7.43		Me	Ac	"
123	8.30		Me	Ac	"
124	7.85		Me	Ac	"
125	7.92		Me	Ac	"
126	8.30		Me	Ac	"
127	7.72		Me	Ac	"
128	8.40		Me	Ac	"
129	7.52		Me	Ac	"

Table 5. Predicted biological activity (pIC_{50}) with the five models

		Predicted pIC_{50}				
Mol ID	**Exp. pIC_{50}**	**Model1**	**Model2**	**Model3**	**Model4**	**Model5**
1	6.21	5.95	5.91	5.91	5.68	5.89
2	4.92	5.36	5.51	5.52	5.03	4.81
3	5.36	5.53	5.64	5.64	5.22	5.23
4	5.28	5.71	5.87	5.87	5.42	5.33
5	5.48	6.00	5.87	5.87	5.73	5.72
6	5.91	5.96	5.86	5.86	5.69	6.23
7	5.85	5.96	5.90	5.90	5.69	6.20
9	5.11	6.04	5.68	5.67	6.18	5.60
10	6.22	5.84	5.74	5.74	5.95	5.94
11	6.23	5.65	5.54	5.54	5.75	5.72
12	5.39	5.73	5.58	5.57	5.76	5.35
14	5.63	5.91	5.78	5.77	5.96	6.33
15	6.80	6.95	6.55	6.56	6.39	5.89
16	6.48	6.48	6.58	6.58	6.27	6.84
18	5.85	6.85	6.68	6.67	6.68	6.39
19	6.52	6.48	6.63	6.62	6.66	6.70
20	6.52	6.96	6.78	6.78	6.79	6.70
22	7.07	7.14	7.20	7.21	6.86	6.93
23	5.26	5.79	5.90	5.91	5.27	5.88
24	6.84	6.14	6.79	6.79	6.08	7.06
25	6.26	6.16	5.90	5.91	6.08	5.88
26	6.72	6.35	6.79	6.79	6.48	7.06
27	5.83	6.35	5.90	5.91	6.48	5.88
28	6.53	6.35	5.90	5.91	6.48	5.88
29	6.80	6.50	5.90	5.91	6.60	5.88
31	7.33	6.52	6.79	6.79	6.59	7.06
32	6.74	6.70	7.97	7.96	6.34	7.06
33	7.42	6.44	6.69	6.69	6.56	7.06
34	5.78	6.56	5.95	5.95	6.58	5.97
35	4.87	6.66	5.90	5.91	6.33	5.88
36	6.03	6.61	5.90	5.91	6.31	5.88
38	5.54	5.12	5.16	5.16	5.27	5.24
39	5.11	5.27	5.16	5.16	5.67	5.24
40	5.30	5.07	5.16	5.16	5.21	5.24
41	4.51	4.40	4.42	4.41	4.40	4.60
42	7.35	7.14	7.21	7.21	6.79	7.07
43	8.15	7.34	7.08	7.08	7.54	7.07
45	8.40	7.70	8.40	8.40	7.06	7.07
46	6.35	7.44	7.14	7.15	7.28	7.07
47	5.68	7.13	6.46	6.47	5.95	6.20
48	5.78	5.41	5.71	5.72	5.65	5.55
49	6.76	7.76	7.26	7.28	7.77	7.07
50	6.85	7.17	7.19	7.21	7.20	6.93
52	7.89	7.69	7.19	7.21	7.79	6.93
53	8.05	7.53	7.82	7.84	8.01	8.11
54	8.22	7.64	7.97	7.99	7.75	8.11
55	8.40	7.32	7.75	7.74	7.77	8.11

56	7.47	7.60	7.58	7.56	8.01	7.54
58	8.00	6.86	7.22	7.21	7.81	7.56
59	8.00	7.35	7.30	7.30	7.94	7.59
61	7.74	7.22	7.30	7.29	7.49	7.56
62	6.94	6.55	6.74	6.71	7.28	7.11
63	6.74	7.03	6.82	6.79	7.42	7.14
64	6.94	7.28	7.11	7.07	7.49	7.09
65	7.85	7.01	7.28	7.28	7.36	7.12
66	6.18	6.69	6.80	6.78	6.83	6.67
67	5.58	5.79	5.44	5.34	5.35	5.39
68	6.58	6.81	7.59	7.59	6.61	7.12
69	5.97	7.17	6.64	6.64	7.13	6.39
71	6.99	6.99	7.60	7.57	7.49	7.52
72	6.37	7.23	6.65	6.60	7.02	6.71
73	6.59	6.94	7.20	7.20	7.28	7.17
74	7.19	7.00	7.51	7.50	7.35	7.17
76	7.46	6.70	7.08	7.04	7.02	7.06
77	6.62	7.36	7.22	7.21	7.49	7.34
79	7.55	7.20	7.19	7.18	7.49	7.66
81	7.60	7.51	7.47	7.32	7.36	7.56
82	7.52	7.67	7.83	7.66	7.36	7.57
83	7.80	7.54	7.63	7.68	7.36	7.57
84	8.30	7.28	7.22	7.41	7.36	7.56
85	7.49	7.91	8.12	8.14	7.71	7.87
86	8.40	7.90	7.99	8.06	7.67	7.84
87	6.84	5.90	5.93	5.93	6.75	6.46
88	8.70	7.76	7.96	8.11	7.88	8.02
89	7.80	7.32	7.38	7.52	7.33	7.51
90	7.04	6.53	6.53	6.54	6.52	6.33
91	7.82	6.89	7.13	7.14	7.33	7.51
92	7.89	7.08	7.41	7.42	7.09	7.51
93	7.29	7.55	7.71	7.57	7.33	7.51
94	7.72	7.94	8.10	8.06	8.11	8.18
95	7.57	7.53	7.57	7.49	7.33	7.51
96	7.66	7.39	7.37	7.25	7.33	7.51
97	7.89	7.87	8.02	8.06	7.92	8.02
98	7.89	7.78	7.78	7.76	7.63	7.77
99	7.74	7.66	7.48	7.39	7.33	7.51
100	7.51	7.83	7.88	7.88	7.80	7.92
102	7.43	7.62	7.42	7.15	7.33	7.51
103	5.75	7.27	6.73	6.58	7.33	7.51
104	6.91	7.93	8.07	8.12	8.09	8.16
105	6.23	7.66	7.57	7.57	7.33	7.51
106	8.30	7.44	7.48	7.60	7.36	7.57
107	8.70	8.05	8.16	8.19	8.12	8.22
108	8.22	7.78	7.68	7.66	7.36	7.57
111	6.80	7.01	6.91	7.02	6.81	7.06
112	6.36	6.62	6.67	6.68	6.99	6.66
113	7.96	7.61	7.57	7.60	7.57	7.71
114	7.31	7.35	7.08	7.07	6.81	7.06
115	5.96	6.69	6.47	6.55	6.54	6.46
117	6.87	7.21	6.99	7.10	7.02	7.06
118	7.13	6.73	6.98	7.07	6.93	7.06

119	5.71	6.55	6.68	6.77	6.73	6.91
120	7.29	7.29	7.18	7.18	7.30	7.11
121	7.68	7.96	7.87	7.90	7.78	7.71
122	7.43	7.96	7.68	7.70	7.78	7.71
123	8.30	7.82	7.66	7.69	7.78	7.71
125	7.92	7.80	7.85	7.87	7.78	7.71
128	8.40	7.15	7.37	7.37	7.49	7.71
Test Set						
8	5.93	5.50	5.59	5.59	5.58	5.25
13	5.74	5.54	5.38	5.37	5.55	5.35
17	5.56	6.66	6.25	6.25	6.46	5.65
21	6.05	7.21	7.11	7.09	6.86	6.36
30	6.68	6.34	6.53	6.53	6.83	7.06
37	5.38	5.29	5.16	5.16	4.87	5.24
44	7.96	7.52	7.34	7.35	7.30	7.07
51	7.07	7.33	8.09	8.11	7.26	8.11
57	8.10	7.70	7.79	7.78	7.75	7.54
60	8.22	7.33	7.76	7.78	7.88	7.57
70	6.79	6.81	7.21	7.18	7.49	7.19
75	7.28	7.20	7.43	7.43	7.49	7.61
78	7.19	7.36	7.47	7.46	7.49	7.59
80	6.78	7.64	7.66	7.57	7.36	7.56
101	6.91	7.57	7.35	7.22	7.33	7.51
109	6.24	6.58	6.65	6.64	6.81	7.06
110	6.02	6.33	6.49	6.61	6.75	6.46
116	7.20	7.35	7.00	7.11	7.02	7.06
124	7.85	7.60	7.90	7.93	7.56	7.71
126	8.30	7.63	7.64	7.64	8.10	8.31
129	7.52	7.49	7.18	7.18	7.78	7.71

Table 7. Correlation plot of descriptors that appear in any of the five models.

	I_6	Ip	MM (R_5)	MM (R_8)	logP (R_2)	logP (R_6)	logP (R_8)	BL (R_2)	BL (R_6)	MR (R_2)	MR (R_8)	VB1 (R_8)	VB5 (R_2)	NHBA (R_8)	NHBA (R_2)
I_6	1														
Ip	0.58	1													
MM(R_5)	0.31	0.23	1												
MM(R_8)	0.13	0.32	0.18	1											
log P (R_2)	-0.36	-0.45	-0.23	-0.17	1										
log P (R_6)	0.08	0.08	0.00	0.03	-0.08	1									
log P (R_8)	0.18	0.28	0.23	0.73	-0.20	0.03	1								
BL(R_2)	-0.25	-0.38	-0.30	-0.11	0.87	-0.10	-0.13	1							
BL(R_6)	0.15	0.19	0.00	0.07	-0.24	0.92	0.08	-0.20	1						
MR(R_2)	0.84	0.55	0.34	0.31	-0.16	0.05	0.31	-0.03	0.09	1					
MR(R_8)	0.14	0.31	0.19	0.98	-0.17	0.03	0.83	-0.11	0.07	0.32	1				
VB1(R_8)	0.25	0.25	0.26	0.53	-0.21	0.02	0.60	-0.06	0.08	0.35	0.55	1			
VB5 (R_2)	0.84	0.59	0.22	0.26	-0.23	0.06	0.28	-0.08	0.13	0.93	0.27	0.32	1		
NHBA (R_8)	-0.21	-0.07	-0.14	0.17	0.15	-0.02	-0.51	0.07	-0.05	-0.14	0.01	-0.27	-0.18	1	
NHBA (R_2)	0.66	0.51	0.21	0.23	-0.59	0.02	0.27	-0.31	0.16	0.66	0.23	0.39	0.74	-0.20	1

Model 6 :

The following equation was generated replacing $MM(R_5)$ with indicator variable I_5 (1 for presence and 0 for the absence of Methyl). Apart from compound 66 and 67, all substituents at R_5 are either H or Me. Hence it is possible that $MM(R_5)$ appearing in all 5 models to act as surrogates for the presence or absence of at this position. Hence Model 6 has been generated to check if it is the case.

$pIC_{50} = 4.855 + 0.758I_6 + 0.364I_p - 0.155I_5 - 0.333\log P(R_6) + 0.441\log P(R_8) + 0.036MR(R_2) - 0.328NHBA(R_2) - 0.570NHBA(R_8)$

$r^2 = 0.574$; $r_a^2 = 0.540$; $s = 0.677$; $F = 16.694$

The result further emphasizes the absence of methyl/substitution at R_5 to be appropriate for CDK4 inhibition.