Supplementary Materials

PPIase protein cyclophilin J inhibitors derived from 2,3-quinoxaline-6 amine exhibit antitumor activity

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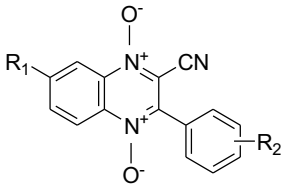
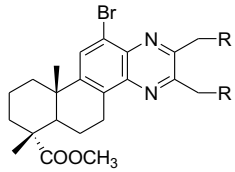
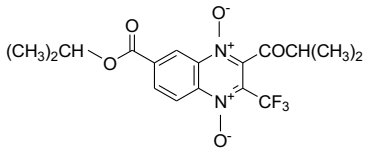
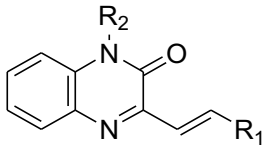
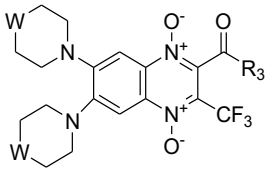
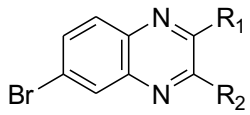
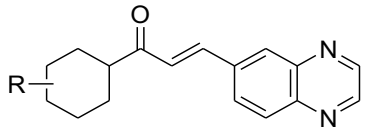
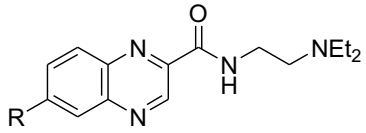
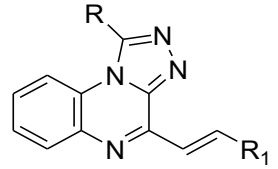
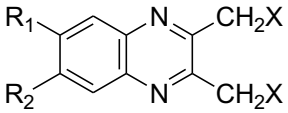
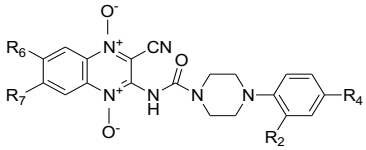
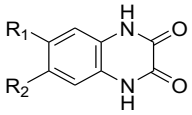
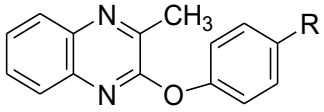
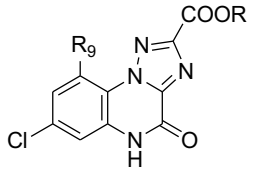
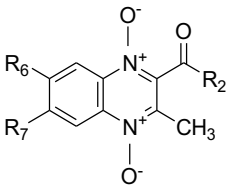
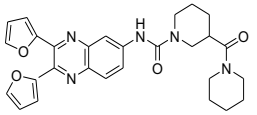
1. SUPPLEMENTARY TABLE

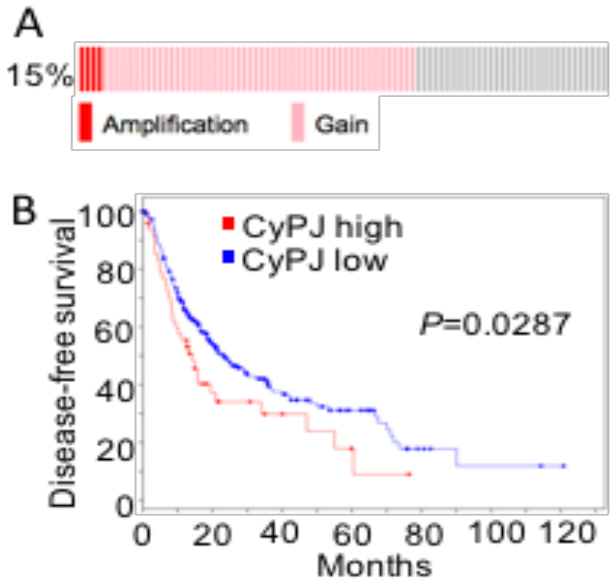
Supplementary Table S1. List of biological active quinoxaline-containing compounds identified in the last decade

Compounds	Activities	References
	Antitumor	1
	Antitumor	2
	Trypanothione reductase inhibitors (IC_{50}=2.42 ± 0.5)	3
	Antitumor	4
	Treatment of multidrug-resistant and latent tuberculosis	5
	Antitumor and antimicrobial	6

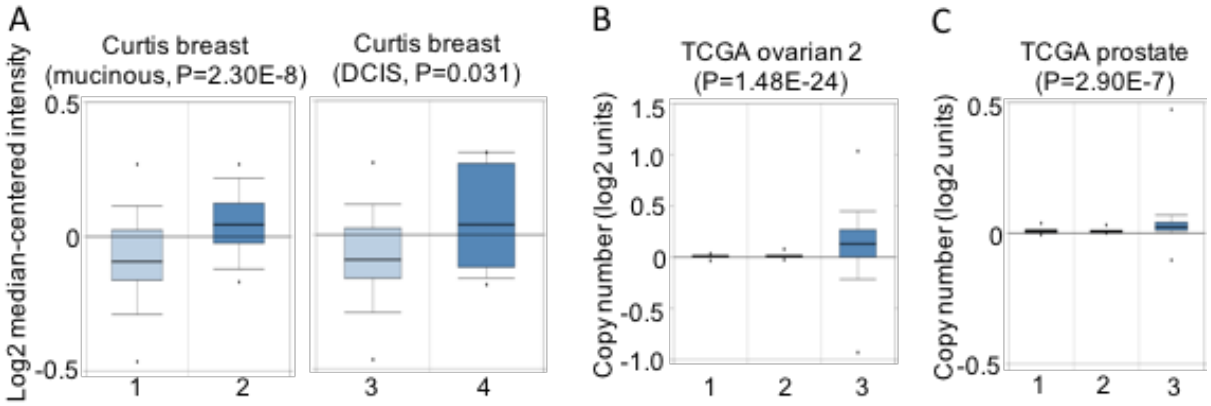
	Inhibitors of breast cancer	7
	Melanoma-targeting probes	8
	Anticonvulsant	9
	Antibacterial and antifungal	10
	Antiplasmodial and leishmanicidal	11
	Neuropharmacological activities	12
	Antimicrobial	13
	(*R,S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) receptor antagonists	14
	Antimycobacterial	15
	JSP-1 inhibitor (2.25 μM)	16

Note: JSP-1, Jnk stimulatory phosphatase-1.

2. SUPPLEMENTARY FIGURES



Supplementary Figure S1. The *CyPJ* gene is frequently altered in HCC samples. (A) The *CyPJ* gene was gained or amplified in 15% of TCGA HCC samples (n=370). The data were retrieved from the cBioPortal for Cancer Genomics (17, 18) as of September 21, 2017. (B) High copy number of the *CyPJ* gene was positively correlated with poor disease-free survival in the above TCGA cohort (n=370).



Supplementary Figure S2. *CyPJ* is altered in breast, ovarian, and prostate cancers. (A) The *CyPJ* gene expression was upregulated in breast ductal carcinoma *in situ* (DCIS) and breast mucinous carcinoma from the Curtis breast cohort (19). For the Curtis breast (mucinous), 1, normal breast (n=144); 2, mucinous breast carcinoma (n=46). For the Curtis breast (DCIS), 3, normal breast (n=144); 4, DCIS (n=10). (B and C) The copy number of the *CyPJ* gene was remarkably higher in TCGA ovarian cancer (B) and TCGA prostate cancer (C). For TCGA ovarian cancer, 1, blood (n=431); 2, ovary (n=130); 3, ovarian cystadenocarcinoma (n=607). For TCGA prostate, 1, blood (n=148); 2, prostate gland (n=61); 3, acinar prostate adenocarcinoma

(n=126). These data were retrieved from the Oncomine (www.oncomine.com) with default parameters (20).

3. SUPPLEMENTARY STRUCTURE DATA OF IDENTIFIED COMPOUNDS

_N_-(2,3-diphenylquinoxalin-6-yl)-2-phenylacetamide (ZX-J-19a)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.54 (br.s, 1H, CONH), 8.24 (d, *J*=2.1 Hz, 1H, H-5), 8.07 (d, *J*=9.0 Hz, 1H, H-8), 7.85 (dd, *J*=9.0, 2.1 Hz, 1H, H-7), 7.28～7.50 (m, 15H, H-$PhCH_2$×5, H-diphenyl×10), 3.84 (s, 2H, H-$PhCH_2$). HRMS(ESI+): Calculated for $C_{28}H_{21}N_3O$, $[M+H]^+$416.1685. Found 416.1663.

_N_-(2,3-diphenylquinoxalin-6-yl)pivalamide (ZX-J-19b)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.31 (d, *J*=1.5 Hz, 1H, H-5), 8.11 (d, *J*=9.1 Hz, 1H, H-8), 7.99 (dd, *J*=9.1,1.5 Hz, 1H, H-7), 7.65 (br.s, 1H, CONH), 7.50 (m, 4H, H- diphenyl-3`, 5`, 3``, 5``), 7.30 (m, 6H, H-diphenyl-2`, 4`, 6`, 2``, 4``, 6``), 1.38 (s, 9H, $(CH_3)_3CCO$). HRMS(ESI+): Calculated for $C_{25}H_{23}N_3O$, $[M+H]^+$382.1841. Found 382.1875.

_N_-(2,3-diphenylquinoxalin-6-yl)-4-nitrobenzamide (ZX-J-19c)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.52 (br.s, 1H, CONH), 8.35 (m, 3H, H-5, H-NO_2PhCO×2), 8.12-8.21 (m, 4H, H-8, H-7, H-NO_2PhCO×2), 7.53 (m, 4H, H-diphenyl-3`, 5`, 3``, 5``), 7.35 (m, 6H, H-diphenyl-2`, 4`, 6`, 2``, 4``, 6``). HRMS(ESI+): Calculated for $C_{27}H_{18}N_4O_3$, $[M+H]^+$447.1379. Found 447.1391.

2-chloro-N-(2,3-diphenylquinoxalin-6-yl)acetamide (ZX-J-19d)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.56 (br.s, 1H, CONH), 8.48 (br.s, 1H, H-5), 8.15 (d, *J*=9.0 Hz, 1H, H-8), 7.99 (br.d, *J*=9.0 Hz, 1H, H-7), 7.52 (m, 4H, H-diphenyl-3`, 5`, 3``, 5``), 7.34 (m, 6H, H-diphenyl-2`, 4`, 6`, 2``, 4``, 6``), 4.36 (s, $ClCH_2CO$). HRMS(ESI+): Calculated for $C_{22}H_{16}ClN_3O$, $[M+H]^+$374.0982. Found 374.0971.

3-chloro-_N_-(2,3-diphenylquinoxalin-6-yl)benzamide (ZX-J-19e)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.77 (br.s, 1H, CONH), 8.49 (br.s, 1H, H-5), 8.8 (m, 2H, H-8, H-7), 7.82 (br.s, 1H, H-ClPhCO), 7.72 (d, *J*=7.6 Hz, 1H, H-ClPhCO), 7.26-7.47 (m, 12H, H-PhCO×2, H-diphenyl×10), 7.35 (m, 6H, H-diphenyl-2`, 4`, 6`, 2``, 4``, 6``). HRMS(ESI+): Calculated for $C_{27}H_{18}ClN_3O$, $[M+H]^+$436.1138. Found 436.1155.

2-chloro-_N_-(2,3-diphenylquinoxalin-6-yl)benzamide (ZX-J-19f)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.48 (br.s, 1H, H-5), 8.39 (br.s, 1H, CONH), 8.16 (d, *J*=9.0 Hz, 1H, H-8), 8.07 (br.d, *J*=9.0 Hz, 1H, H-7), 7.80 (d, *J*=7.4 Hz, 1H, H-ClPhCO), 7.18-7.53 (m, 13H, H-PhCO×3, H-diphenyl×10), 7.35 (m, 6H, H-diphenyl-2`, 4`, 6`, 2``, 4``, 6``). HRMS(ESI+): Calculated for $C_{27}H_{18}ClN_3O$, $[M+H]^+$436.1138. Found 436.1161.

4-chloro-_N_-(2,3-diphenylquinoxalin-6-yl)benzamide (ZX-J-19g)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.46 (d, *J*=2.2 Hz, 1H, H-5), 8.29 (br.s, 1H, CONH), 8.16 (d, *J*=9.0 Hz, 1H, H-8), 8.10 (dd, *J*=9.0, 2.2 Hz, 1H, H-7), 7.87 (d, 2H, H-ClPhCO×2), 7.49 (m, 6H, H-ClPhCO×2, H-diphenyl-3`, 5`, 3``, 5``), 7.35 (m, 6H, H-diphenyl-2`, 4`, 6`, 2``, 4``, 6``).HRMS(ESI+): Calculated for $C_{27}H_{18}ClN_3O$, $[M+H]^+$436.1138. Found 436.1127.

***N*-(2,3-diphenylquinoxalin-6-yl)benzamide (ZX-J-19h)**
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.47 (br.s, 1H, H-5), 8.38 (br.s, 1H, CONH), 8.10 (m, 2H, H-8, H-7), 7.91 (m, 2H, H-PhCO×2), 7.26-7.56 (m, 13H, H-PhCO×3, H-diphenyl×10), 7.35 (m, 6H, H-diphenyl-2`, 4`, 6`, 2``, 4``, 6``). HRMS(ESI+): Calculated for $C_{27}H_{19}N_3O$, $[M+H]^+$402.1528. Found 402.1547.

***N*-(2,3-diphenylquinoxalin-6-yl)propionamide (ZX-J-19i)**
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.31 (d, *J*=1.8 Hz, 1H, H-5), 8.10 (d, *J*=9.1 Hz, 1H, H-8), 7.99 (dd, *J*=9.1, 1.8 Hz, 1H, H-7), 7.68 (br.s, 1H, CONH), 7.50 (m, 4H, H- diphenyl-3`, 5`, 3``, 5``), 7.34 (m, 6H, H-diphenyl-2`, 4`, 6`, 2``, 4``, 6``), 2.48 (q, *J*=7.7 Hz, 2H, CH_3CH_2CO), 1.29 (t, *J*=7.7 Hz, 3H, CH_3CH_2CO). HRMS(ESI+): Calculated for $C_{23}H_{19}N_3O$, $[M+H]^+$354.1528. Found 354.1557.

***N*-(2,3-diphenylquinoxalin-6-yl)octanamide (ZX-J-19j)**
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.30 (d, *J*=1.8 Hz, 1H, H-5), 8.11 (d, *J*=9.0 Hz, 1H, H-8), 7.99 (br.d, *J*=9.0 Hz, 1H, H-7), 7.53 (br.s, 1H, CONH), 7.50 (m, 4H, H- diphenyl-3`, 5`, 3``, 5``), 7.34 (m, 6H, H-diphenyl-2`, 4`, 6`, 2``, 4``, 6``), 2.45 (t, *J*=7.4 Hz, 2H, $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CO$), 1.61 (br.s, 4H, $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CO$), 1.25 (br.s, 6H, $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CO$), 0.87 (t, *J*=7.4 Hz, 3H, $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CO$). HRMS(ESI+): Calculated for $C_{28}H_{29}N_3O$, $[M+H]^+$424.2311. Found 424.2337.

***N*-(2,3-diphenylquinoxalin-6-yl)acetamide (ZX-J-19k)**
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.33 (br.s, 1H, H-5), 8.11 (d, *J*=9.1 Hz, 1H, H-8), 8.00 (dd, *J*=9.1, 1.8 Hz, 1H, H-7), 7.61 (br.s, 1H, CONH), 7.47(m, 4H, H- diphenyl-3`, 5`, 3``, 5``), 7.31 (m, 6H, H-diphenyl-2`, 4`, 6`, 2``, 4``, 6``), 2.28 (s, 3H, CH_3CO). HRMS(ESI+): Calculated for $C_{22}H_{17}N_3O$, $[M+H]^+$340.1372. Found 340.1394.

***N*-(2,3-diphenylquinoxalin-6-yl)butyramide (ZX-J-19l)**
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.31 (br.s, 1H, H-5), 8.10 (d, *J*=9.0 Hz, 1H, H-8), 7.99 (br.d, *J*=9.0 Hz, 1H, H-7), 7.64 (br.s, 1H, CONH), 7.50 (m, 4H, H- diphenyl-3`, 5`, 3``, 5``), 7.30 (m, 6H, H-diphenyl-2`, 4`, 6`, 2``, 4``, 6``), 2.43 (t, *J*=7.4 Hz, 2H, $CH_3CH_2CH_2CO$), 1.81 (sext, *J*=7.4 Hz, 2H, $CH_3CH_2CH_2CO$), 1.04 (t, *J*=7.4 Hz, 3H, $CH_3CH_2CH_2CO$). HRMS(ESI+): Calculated for $C_{24}H_{21}N_3O$, $[M+H]^+$368.1785. Found 368.1766.

***N*-(2, 3-di(furan-2-yl)quinoxalin-6-yl) pivalamide (ZX-J-19m)**
^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (br.s, NH), 8.57 (d, J = 1.7 Hz, 1H, H-5), 8.08 (dd, J = 9.3, 2.3 Hz, 1H, H-7), 8.01 (d, J = 8.9 Hz, 1H, H-8), 7.88, (m, 2H, H-furanyl-5`, 5``), 6.70 (m, 4H, H- furanyl-3`, 4`, 3``, 4``),1.30 (s, 9H, CH_3×3). HRMS(ESI+): Calculated for $C_{21}H_{19}N_3O_3$, $[M+H]^+$362.1426. Found 362.1451.

***N*-(2,3-di(furan-2-yl)quinoxalin-6-yl)butyramide (ZX-J-19n)**
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.43 (br.s, NH), 8.53 (d, J = 2.1 Hz, 1H, H-5), 8.03 (d, J = 9.1 Hz, 1H, H-8), 7.90 (dd, J = 8.9, 2.3 Hz, 1H, H-7), 7.87 (m, 2H, H-furanyl-5`, 5``), 6.69 (m, 4H, H-furanyl-3`, 4`, 3``, 4``), 2.41 (t, J = 7.4 Hz, 2H, -$CH_2CH_2CH_3$), 1.67 (m, 2H, -

$CH_2CH_2CH_3$), 0.96 (t, J = 7.1 Hz, 3H, -$CH_2CH_2CH_3$). HRMS(ESI+): Calculated for $C_{20}H_{17}N_3O_3$, $[M+H]^+$348.1270. Found 348.1279.

***N*-(2,3-di(furan-2-yl)quinoxalin-6-yl)octanamide (ZX-J-19o)**
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.43 (br.s, NH), 8.53 (d, J = 2.1 Hz, 1H, H-5), 8.02 (d, J = 9.1 Hz, 1H, H-8), 7.90 (dd, J = 9.1, 2.1 Hz, 1H, H-7), 7.87 (m, 2H, H-furanyl-5`, 5``), 6.69 (m, 4H, H-furanyl-3`, 4`, 3``, 4``), 2.42 (t, J = 7.4 Hz, 2H, -$CH_2CH_2(CH_2)_4CH_3$), 1.65 (m, 2H, -$CH_2CH_2(CH_2)_4CH_3$), 1.30 (m, 8H, -$CH_2CH_2(CH_2)_4CH_3$), 0.96 (t, J = 6.9, 3H, -$CH_2CH_2(CH2)_4CH_3$). HRMS(ESI+): Calculated for $C_{24}H_{25}N_3O_3$, $[M+H]^+$404.1896. Found 404.1917.

2-chloro-*N*-(2,3-di(furan-2-yl)quinoxalin-6-yl)benzamide (ZX-J-19p)
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.09 (br.s, N*H*), 8.64 (d, J = 1.3 Hz, 1H, H-5), 8.10 (d, J = 9.2 Hz, 1H, H-8), 8.04 (dd, J = 9.1, 1.9 Hz, 1H, H-7), 7.89 (m, 2H, H-furanyl-5`, 5``), 7.70 (dd, J = 7.4, 1.7 Hz, 1H, H-Ph-6```), 7.61 (dt, J = 7.2, 1.7 Hz, 1H, H-Ph-4```), 7.55 (dd, J = 7.8, 1.8 Hz, 1H, H-Ph-3```), 7.51 (dt, J = 7.3, 1.6 Hz, 1H, H-Ph-5```), 6.72 (m, 4H, H-furanyl-3`, 4`, 3``, 4``). HRMS(ESI+): Calculated for $C_{23}H_{14}ClN_3O_3$, $[M+H]^+$416.0727. Found 416.0755.

***N*-(2,3-di(furan-2-yl)quinoxalin-6-yl)-4-nitrobenzamide (ZX-J-19q)**
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.07 (br.s, NH), 8.70 (d, J = 1.4 Hz, 1H, H-5), 8.43 (d, J = 8.8 Hz, 2H, H-Ph-3```, 5```), 8.27 (d, J = 8.8, Hz, 1H, H-Ph-2```, 6```), 8.17 (dd, J = 9.1, 1.9 Hz, 1H, H-7), 8.11 (d, J = 8.7 Hz, 1H, H-8), 7.90 (m, 2H, H-furanyl-5`, 5``), 6.74 (m, 4H, H-furanyl-3`, 4`, 3``, 4``). HRMS(ESI+): Calculated for $C_{23}H_{14}N_4O_5$, $[M+H]^+$427.0964. Found 427.0947.

***N*-(2,3-di(furan-2-yl)quinoxalin-6-yl)benzamide (ZX-J-19r)**
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.79 (br.s, NH), 8.70 (d, J = 2.3 Hz, 1H, H-5), 8.18 (dd, J = 9.2, 2.3 Hz, 1H, H-7), 8.08 (d, J = 9.0 Hz, 1H, H-8), 8.03 (d, J = 6.8, 1.6 Hz, 2H, H-Ph-2```, 6```), 7.90 (m, 2H, H-furanyl-5`, 5``), 7.61 (m, 3H, H-Ph-3```, 4```, 5```), 6.72 (m, 4H, H-furanyl-3`, 4`, 3``, 4``). HRMS(ESI+): Calculated for $C_{23}H_{15}N_3O_3$, $[M+H]^+$382.1113. Found 382.1136.

***N*-(2,3-di(furan-2-yl)quinoxalin-6-yl)-2-phenylacetamide (ZX-J-19s)**
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.74 (br.s, NH), 8.51(d, J = 2.1 Hz, 1H, H-5), 8.04 (d, J = 9.0 Hz, 1H, H-8), 7.92 (dd, J = 8.9, 2.2 Hz, 1H, H-7), 7.88 (m, 2H, H-furanyl-5`, 5``), 7.33 (m, 5H, H-Ph-2```, 3```, 4```, 5```), 6.69 (m, 4H, H-furanyl-3`, 4`, 3``, 4``), 3.77 (s, 2H, -$COCH_2Ph$). HRMS(ESI+): Calculated for $C_{24}H_{17}N_3O_3$, $[M+H]^+$396.1270. Found 396.1287.

4-chloro-*N*-(2,3-di(1H-pyrrol-2-yl)quinoxalin-6-yl)benzamide(ZX-J-19t)
^{1}H NMR (300 MHz，$CDCl_3$) δ: 9.73 (br.s, 1H, -pyrrol-NH), 9.53 (br.s, 1H, -pyrrol-NH), 8.21 (br.s, 1H, H-5), 8.17(br.s, 1H, CONH), 7.82 (m, 3H, H-8, H-ClPhCO×2), 7.47 (m, 3H, H-7, H-ClPhCO×2), 6.90 (m, 4H, H-dipyrrol-2`, 5`, 2``, 5``), 6.27 (m, 2H, H-dipyrrol-4`, 4``); ESI-MS *m/z*: 414.2 ($[M+H]^+$), 849.1 ($[2M+Na]^+$), 412.3 ($[M-H]^-$). HRMS(ESI+): Calculated for $C_{23}H_{16}ClN_5O$, $[M+H]^+$414.1043. Found 414.1061.

***N*-(2,3-di(1H-pyrrol-2-yl)quinoxalin-6-yl)acetamide (ZX-J-19u)**
^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.78 (br.s, 1H, -pyrrol-NH), 9.59 (br.s, 1H, -pyrrol-NH), 8.13 (d, *J*=2.5 Hz, 1H, H-5), 7.79 (d, *J*=9.2 Hz, 1H, H-8), 7.64(br.d, *J*=9.2 Hz, 1H，H-7), 7.50 (br.s, 1H,

CONH), 6.90 (m, 4H, H-dipyrrol-2`, 5`, 2``, 5``), 6.26 (m, 2H, H-dipyrrol-4`, 4``), 2.17 (s, 3H, CH_3CO); ESI-MS *m/z*: 318.2 ($[M+H]^+$), 340.1 ($[M+Na]^+$), 657.1 ($[2M+Na]^+$), 316.0 ($[M-H]^-$). HRMS(ESI+): Calculated for $C_{18}H_{15}N_5O$, $[M+H]^+$318.1277. Found 318.1289.

2-chloro-N-(2,3-di(1H-pyrrol-2-yl)quinoxalin-6-yl)acetamide (ZX-J-19v)
^1H NMR (300 MHz, $CDCl_3$) δ: 9.75 (br.s, 1H, -pyrrol-NH), 9.59 (br.s, 1H, -pyrrol-NH), 8.47 (br.s, 1H, CONH), 8.25 (d, *J*=2.5 Hz, 1H, H-5), 7.85 (d, *J*=9.3 Hz, 1H, H-8)，7.64(dd, *J*=9.3, 2.5 Hz, 1H, H-7)，6.98 (m, 4H, H-dipyrrol-2`, 5`, 2``, 5``)，6.28 (m, 2H, H-dipyrrol-4`, 4``), 4.22 (s, 2H, H-$ClCH_2CO$); HRMS(ESI+): Calculated for $C_{18}H_{14}ClN_5O$, $[M+H]^+$352.0887. Found 352.0899.

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