

Supplementary material

to

Ubiquitous purine sensor modulates diverse signal transduction pathways in bacteria

by

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Gavira, Igor B. Zhulin and Tino Krell

Figure S1. Schematic representation of the the molecular detail of uric acid recognition by McpH-LBD. Hydrogen bonds are shown as dotted lines and distances are indicated in Å. Hydrophobic interactions are shown as spiked arks. The amino acids that are part of the purine binding motif are labelled in red. The Figure was generated using Ligplot (1).

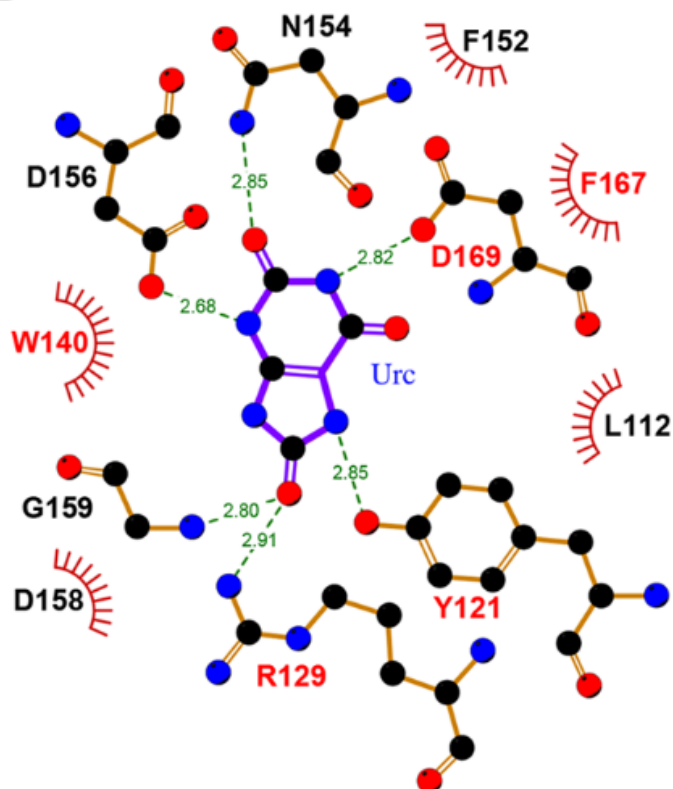


Figure S2. Phyletic distribution of purine binding dCache_1 domains. Blue dots indicate domains found in the RefSeq database; orange dots – domains found when the search was extended to include protein sequences from the NCBI non-redundant database. The updated taxonomy is used (2).

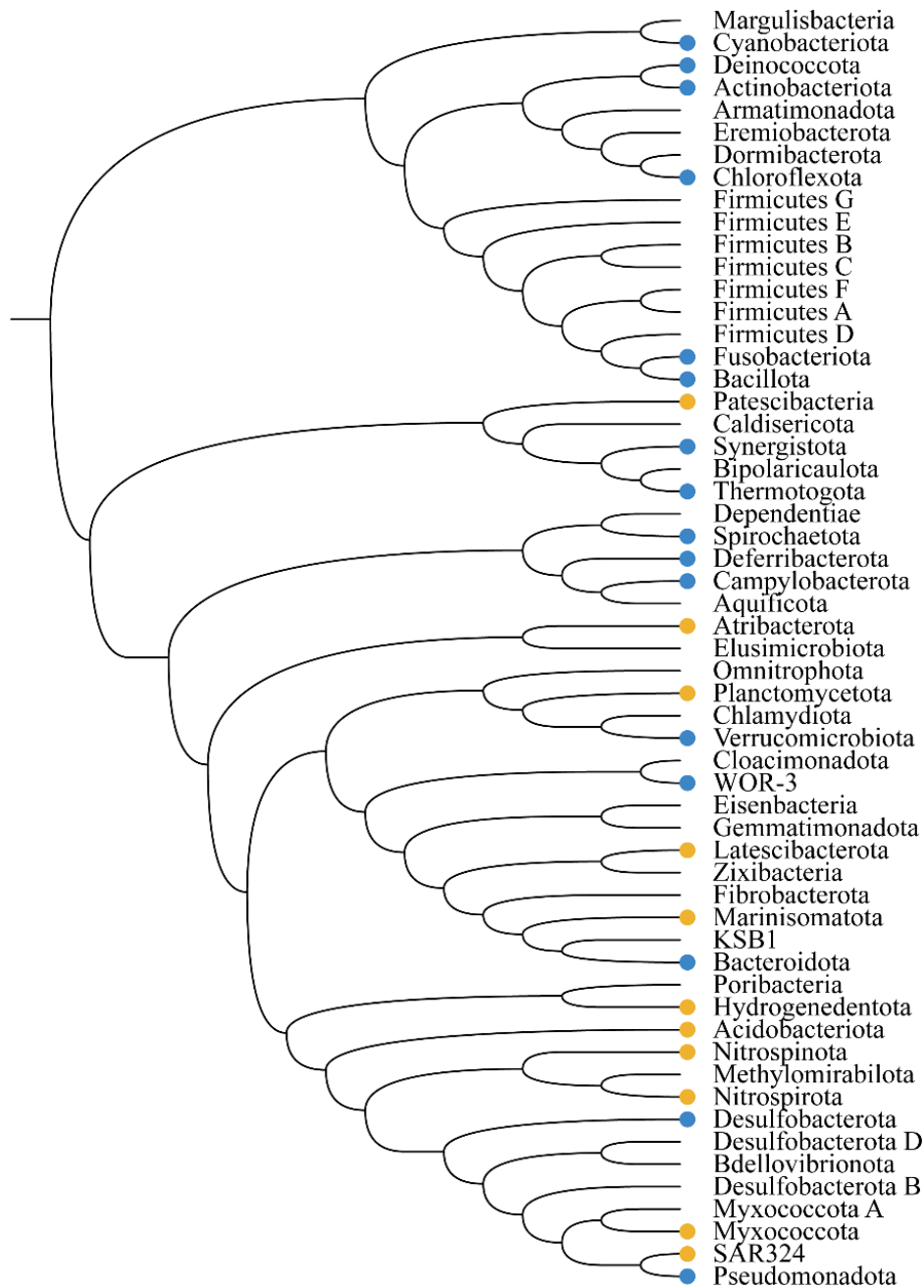


Figure S3. Microcalorimetric titrations of the McpH-LBD mutants that were used to derive the dissociation constants as provided in Table 1. Proteins at 9 to 18 μM were placed into the sample cell and titrated with 12.8 μl aliquots of 2 mM adenine made up in dialysis buffer. Upper panels: raw titration data. Lower panels: integrated, concentration-normalized and dilution heat-corrected peak areas and best fit using the “one-binding site model” of the MicroCal version of ORIGIN.

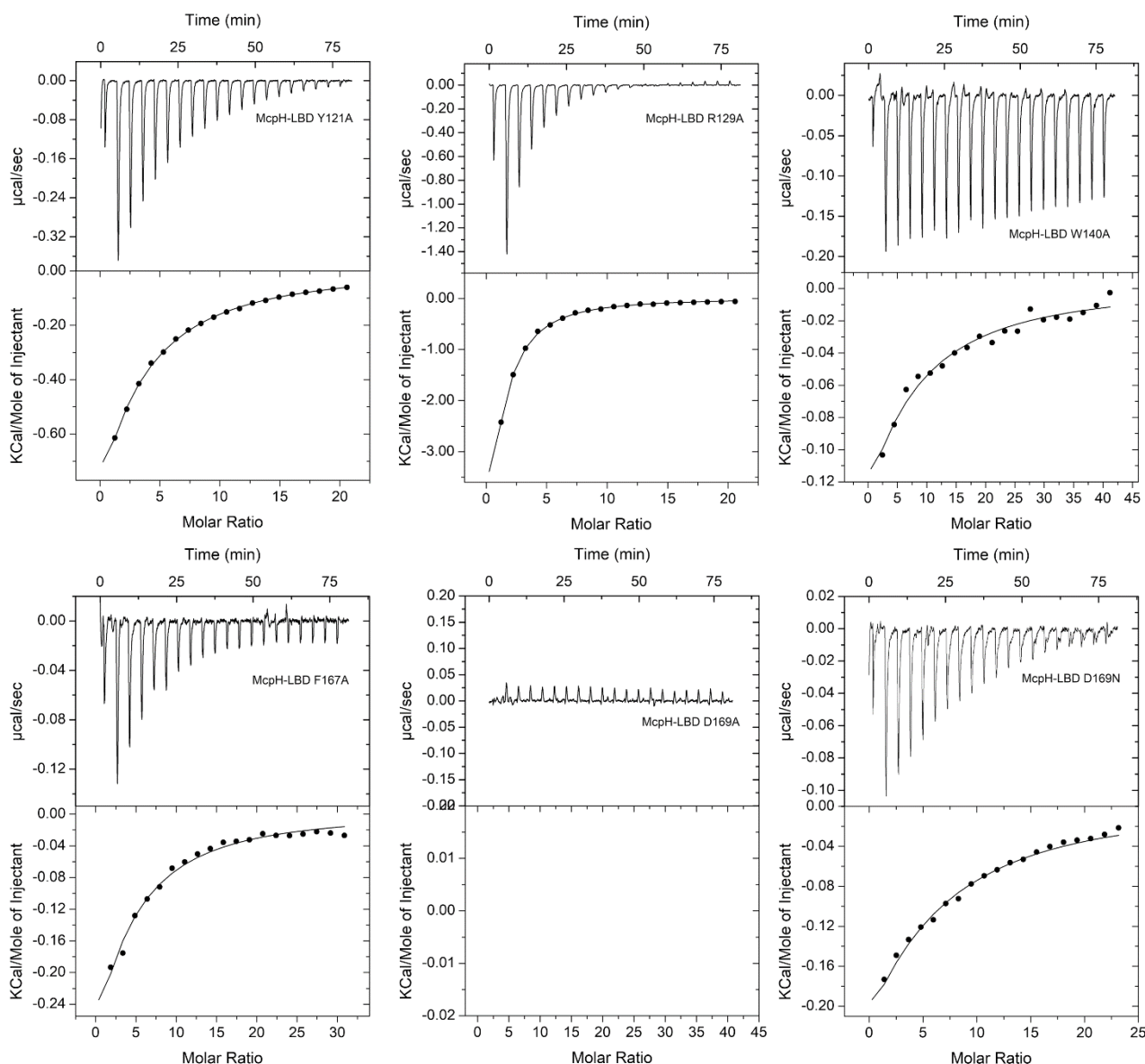


Figure S4. Thermal shift assays of R10 and R13. Changes in the midpoint of protein unfolding (T_m) in the presence of 2 mM ligand as compared to the buffer control. The following compounds were used (from left to right): adenine, adenosine, guanine, guanosine, inosine, xanthine, uric acid, allantoin, hypoxanthine, thymine, cytosine, purine, caffeine, theobromine and theophylline.

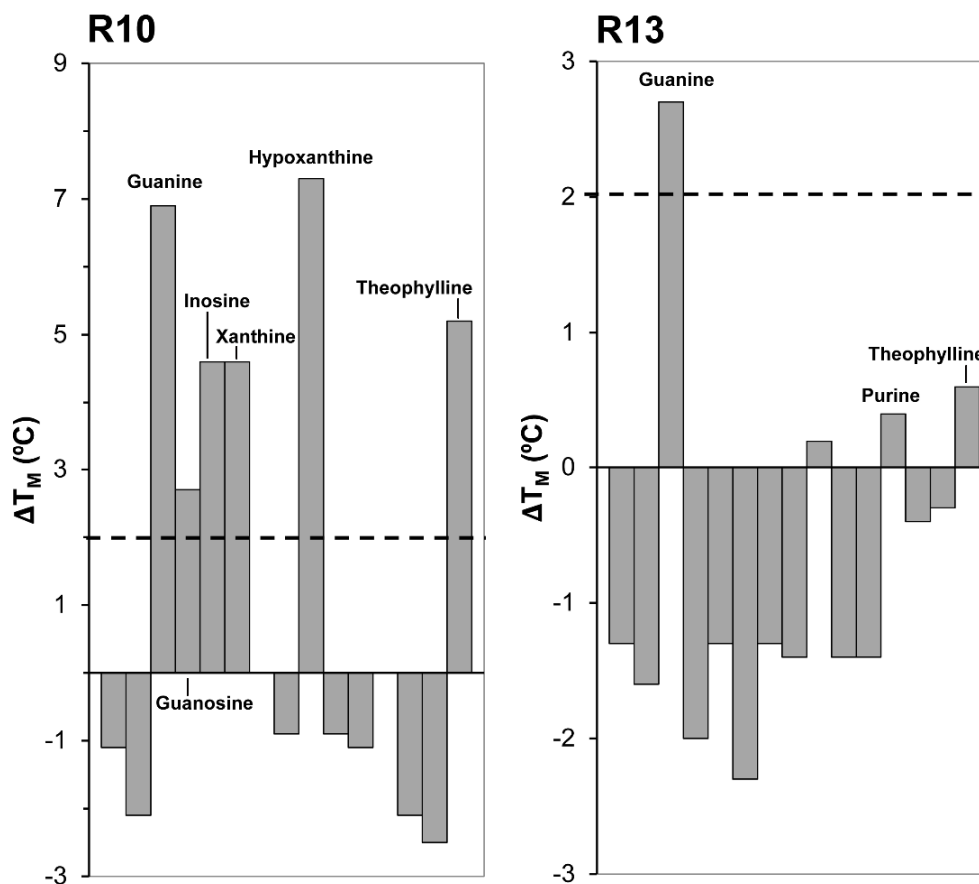


Figure S5. Structure of ligands analysed in this study.

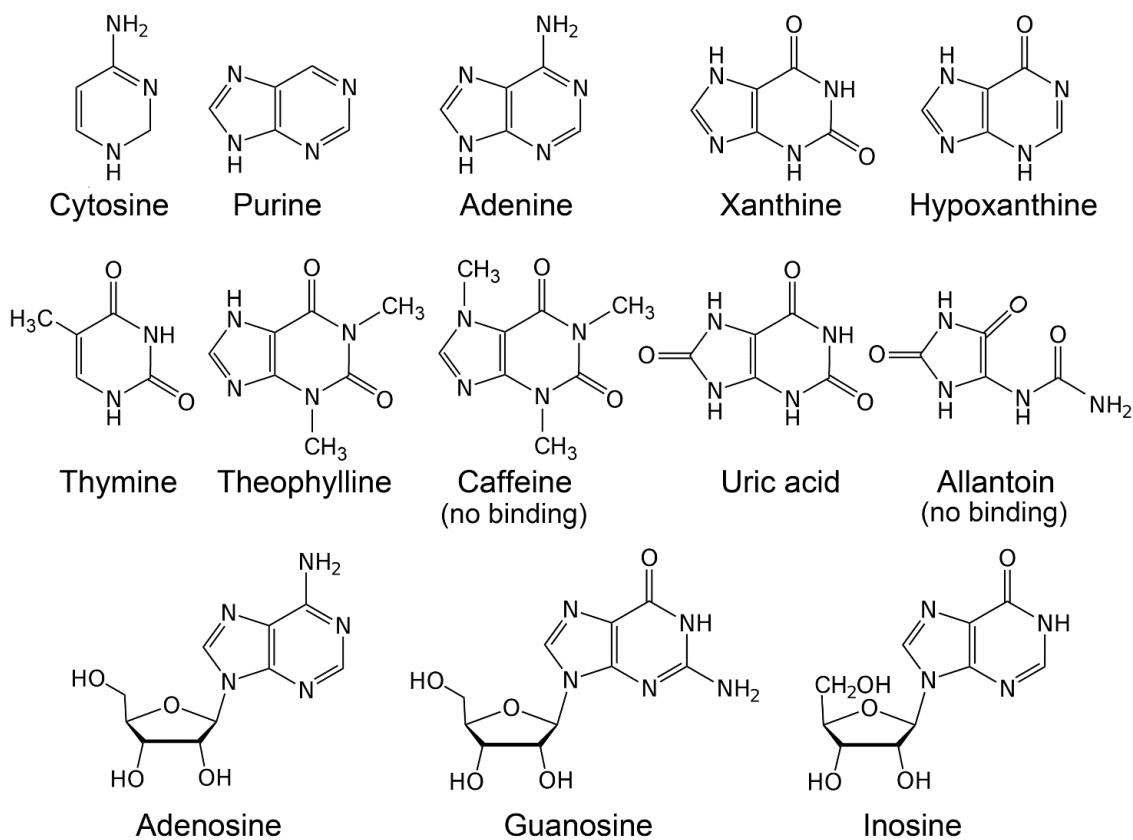


Figure S6. Bayesian phylogenetic tree depicted in Figure 6 with proteins annotated.

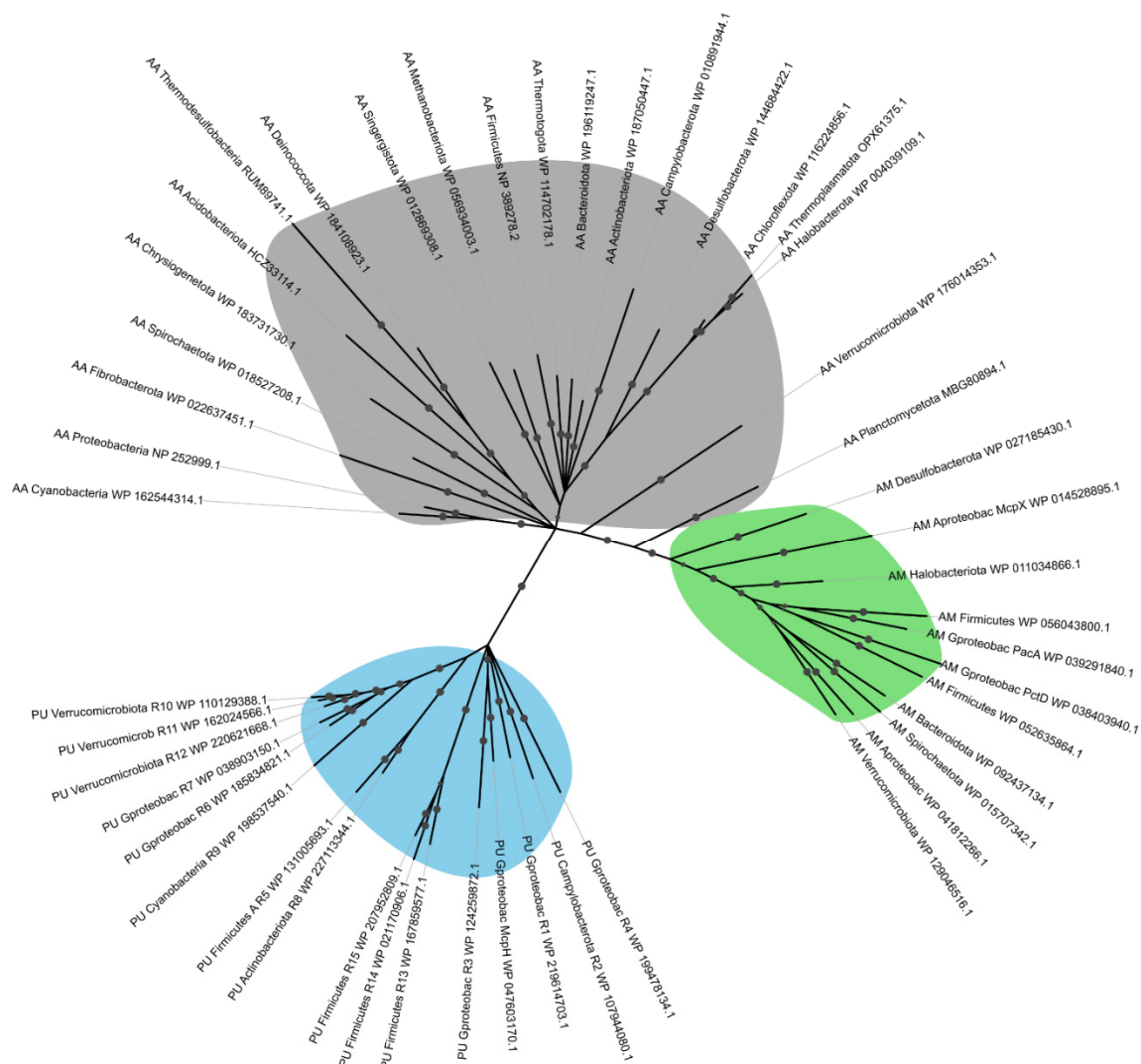


Figure S7. Multiple sequence alignment of amino acid, amine, and purine binding dCache_1 domains. Ligand-binding motifs are shown: purine motif (cyan), amine motif (green), amino acid motif (grey). Gproteobac: Gammaproteobacteria. Extensions R1, R2 etc. mark the proteins that have been analysed in this study (Table 2).

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AA_Thermotogota_WP_114702178.1     ----G-----KELGTTSLLSIATSGTKN-LENFLQGYVNLV
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PU_Campylobacterota_R2_WP_107944080.1	-----KTL-NYYTND-----KILKQLSKDN-
PU_Firmicutes_R13_WP_167859577.1	-----VSN-RYWEGEG-----GTVLRTMSRSD-
PU_Firmicutes_R15_WP_207952809.1	-----MTG-SYWIEG-----KQMSKILSQTN-
PU_Firmicutes_R14_WP_021170906.1	-----VTN-QYWEDN-----KVVKPLSKTS-
PU_Gproteobac_R4_WP_199478134.1	-----KSGLEFLGYD-----QKFFRTPLADY-
AA_Proteobacteria_NP_252999.1	-----RSRPWYKDAVA--GGLTLTEPYVDAA-TQE--LIITAATPVKA-A---GNT
AA_Cyanobacteria_WP_162544314.1	-----RKRPWYQAAS--GKLTLETPYIAAS-SGE--LNITAAAPRYQ-G---GQL
AA_Actinobacteriota_WP_187050447.1	-----RQRDWYQSALKQ--KNKTIWTEPYTDQA-TNE--LVITAAKAIYDDR---DEL
AA_Bacteroidota_WP_196119247.1	-----RTRSWYKATVNN--NEKIIWTEPYVDAGDLGN--VIVTVAKAIHK-N---DSL

AA_Thermotogota_WP_114702178.1
 AA_Methanobacteriota_WP_056934003.1
 AA_Firmicutes_NP_389278.2
 AA_Desulfobacterota_WP_144684422.1
 AA_Chloroflexota_WP_116224856.1
 AA_Halobacterota_WP_004039109.1
 AA_Thermoplasmata_OPX61375.1
 AA_Spirochaetota_WP_018527208.1
 AA_Singergistota_WP_012869308.1
 AA_Verrucomicrobiota_WP_176014353.1
 AA_Planctomycetota_MBG80894.1
 AA_Campylobacterota_WP_010891944.1
 AA_Chrysiogenetota_WP_183731730.1
 AA_Acidobacteriota_HCZ33114.1
 AA_Deinococcota_WP_184108923.1
 AA_Thermodesulfobacteria_RUM89741.1
 AA_Fibrobacterota_WP_022637451.1
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 AM_Aproteobac_WP_041812266.1
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 PU_Actinobacteriota_R8_WP_227113344.1
 PU_Cyanobacteria_R9_WP_198537540.1
 PU_Gproteobac_R7_WP_038903150.1
 PU_Gproteobac_R6_WP_185834821.1
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 PU_Verrucomicrob_R11_WP_162024566.1
 PU_Verrucomicrobiota_R12_WP_220621668.1
 PU_Campylobacterota_R2_WP_107944080.1
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 PU_Firmicutes_R15_WP_207952809.1
 PU_Firmicutes_R14_WP_021170906.1
 PU_Gproteobac_R4_WP_199478134.1

AA_Proteobacteria_NP_252999.1
 AA_Cyanobacteria_WP_162544314.1
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 AM_Gproteobac_PacA_WP_039291840.1
 AM_Halobacteriota_WP_011034866.1
 AM_Spirochaetota_WP_015707342.1

-----TKRPWYVDVAVKN--KGKVIITEPYLDAS-TSD--IVITVAKAVVN-N---GQI
 -----RVRPWYIKAKEN---NGPSYTEPYRDAF-TGK--WVITYSEPVYV-D---GKF
 -----TSRPWYKLAET--PDQVWTEPYKDVV-TGD--MIVTASKAILD-R---QKV
 -----RSPWYQATALAN--PARTSITSAYMST--TGE--PVISLMHGIQSER---NEL
 -----RDRPWYILAKEN--PGTVMITEPYQSLT-TSD--INVGIVTALVDQT---GEV
 -----RERPWYILAKEH--PGEVMVTEPYSSVT-TPD--VNIGVTALDDED---GEV
 -----RERPWYQLAMET--PGEVRITDPYSAVT-TDD--VNIGIVLALMD-N---GTV
 -----REGRWYQTAQSQ--TGPFGSDSYVDAH-TGN--LVITAARPLRDQE---GEI
 -----RKRPWYIQAVQE---DKVILTAPYVDAN-TGG--LVITVATPVKSTS---GKL
 -----RQRGWFKSAAAH--PGETCWSAPYASASLDNK--LVISCSRAIQDAD---GKL
 -----LERDWYRVGVD---GEAGWTEPYDGPV-FGS--LLVTYSSPVIQ-N---GKV
 -----KTKDWYQEAALKT---NDIFVTPAYLDTV-LKQ--YVITYSKAIYK-D---GKI
 -----FERPWYLRATES--PGQIAWTDLYDEII-TGI--PQISAVVTVHDPE--SLEP
 -----RTRPWYLAGAAA---PAPTWTEPYAFYT-TQD--PGITYTLVPRD-T---TGL
 -----RTRPWYTLAVAT--PGITVWTPPYTFAS-SGQ--PGVTVARAVDA-G---ADG
 -----RKRPWFRSSSSE---RRVFWSPVYRFYS-TGK--PGVTASVSWAESG--NPPR
 -----TQRPWFAPLFES---PTKQWSEVVNLDKAE--LTITHMLPVFSPQ---NTL
 -----PQADWFLIPKEI---RRPIWSEPYFDEG-GGN-VVMSYISIPFREEDGRKRF
 -----YAAEWYGLAOKS---GKGAITQPYLAEG-TDVPTMTSIAPVMS-N---GRM
 -----GQGDWYLLPQKS---QKDTLIEPYTYAY-NGVPTLLTVAAPIVS-Q---GKL
 -----SDYYQLPKAT---EKDVLTEPYFYEG---VFMVSYVSPIMK-E---GEF
 -----EDWYIVPKAE---RHEYITDPYPYGL-QGRVTMLASLIFPIIH-S---DKF
 -----GAGDYYLLAKHS---NQETVLEPYIYKV-AGRDLVMTSLVVPVNRAD---GTF
 G-----SDGAWYQIPKRT---GHAMVVEPYSYTV-AGRKVLVMSVPIVE-N---GRV
 -----SAAFWYIWMPT---MKEFVTEPLMYPPI-QGKNVYVSMFCPIIT-N---GKF
 -----GDGDWYQIPKRT---KKFALMEPYYYDI-NGERILTSFVYPILDEQ---GKF
 -----EISDWYIVPKQT---LSNVMIEPYIYEV-QGKEVLMTCSPIVI-D---GKY
 KLLPTGVRENEFYACPEN---KRPCIIDPAPYEM-GGKTVMSSFNVPIMV-G---DQF
 -----ATDNWYDFLSK---GKQLEIKLGKDKAS--SV--YNLFIDARFDV-N---GK-
 -----PKDKWYFYGIDS---GAERFINIDIDGAT--GE--LALFIDYRVEK-E---GKL
 -----EQDAWYFYGTYS---PQDLMLSI-FRETN--GE--VKLFVNFQQLN---GR-
 -----SENQWYTYFLKN---DDEYSLNVDNDEAS-NNS--ITVFVNCKIKDDN---GAT
 -----PENTWYFDFLDR---DEAYSLNVDNDEAT-ADE--ITMFINARILDEQ---GST
 -----AQDAWYFRLRAS---ASSYEVNLDRTAD-PSR--TTVFVNYKLLGDG---GRF
 -----PEDKWYFDIRDEKGDGPDYDIEIGVDPEN-RTR--MDIFINYKVFDS---GNF
 -----PNDAWYFYRVKNSAPDKNFVNIDIDTAN-SQO--TVVFVNYKVFDFE---NRF
 -----PRDEWYFRVREM---DEPYEINVDPDMAN-QDA--LTIETINRVRDYA---GNF
 -----PRDAWYFKARDM---DAPYEINVDLDMAN-QDQ--MTIFINRVFDYN---DNF
 -----PRDVWYFRVREM---EKPFIEINVIDIDMAN-NDA--LTVFVNYRVYDYE---GNY
 -----PRDSWYFDVKN---KEVNSLNIQVSEAT--GS--LTLVYNSKVEK-D---GKF
 -----PEDAWYFANVDN---RKPIEIVLDYAIAR--GD--TFVFYNALIGG---AERA
 -----PADKWYFYSFAS---QKRMALNIDYNSR--RD--TFVFVNVLVGD---VESP
 -----YTDKWYFYKALKS---GKKIELNIDYDSIH--NE--TFIFENTLVGD---VRQP
 -----PYKEFYPNFLAK--NKDYELNLQYADQK-----LYINYSREMDPTTGKP

LGVVGGLSLKTLVQIINSIDF--S-GMGYAFVLVSGDGKILVHP-DK-----EQV
 VGVVGSDFSIQMLDQMLKDALN--G-DLGLFITDKSGKVLIIHA-NQ-----DLI
 IGVLGVDISIDTLITMVNQTKF--G-ETGYTVLLDQKGSFVTHP-DK-----EKI
 VGVIGMDIKLKKFSNIINNIQF--G-ENGYLMLLSKKGDVYVYAH-NN-----KML
 IGVVALDFKASELANSLNKNF--G-ENGYSYLLSSDGKTLHV-DE-----EKI
 VGVVGIDVVFSTLMKEAMDIKL--G-KSGYIVLVNQEGVLMLHP-KE-----EYI
 IGVASYDLKLDSAIQSMVNLQKV--P-YKGFALFADASGNLVAHP-SN-----Q--
 VGIAGLDVSLGALTSLIORSQI--G-ETGYVMLVQGDGVILANPRNP-----ETN
 YGVIGADVTLTNLTFISGFDV--G-HSGQLLLVNEQGAILANK-NS-----QLL
 YGVIGADITLVNLTEYLASIES--I-GNQEMILTDRTSGTILASY-NT-----TVL
 YGVVGADITLVGLTDYLRQASE--V-SGRDMLLSDDRGTILAYK-QE-----QLL
 FGVLATDISLGQITEAISYCL--G-EGGYAFVLVNEQESLLAHP-DT-----EXA
 LGVAGIDVLDKLTLSMITSYKV--F-GKGYGFLLDREGNMICH-P-KS-----EMI
 FGVLALDISVEAVIHDFISTQE--M-RRGSAFLNDSGEIIAQE-GM-----DLL
 IGVMAADIALPLQRLKEEAP---EGLSTILASASGRLTAHP-NP-----ALI
 IGVLGVDIPSEDQLNLVAK-----TPGNTFLFDQKKNIFAAT-NK-----ELL
 VGMALDVSILHQLRRIMVDEL--P-SDAELVLLDRNHQLIVSSTGK-----RGV
 RGVAAALDLDLDTAQVMDAQ--T-SRSRCLVVDAGQNALVLPDAFETPEGRRAFL
 TVVVGADVQLRQVASFQGVQI--G-GHGRAFVTDAGQHVIAITS-PT---WPG---NVT
 TVVFALDITLSIQKFLLELQDD--N-KHELLFILNPRDKFFITP-----KYI
 YGAAIVDVKLGRHLHAFLQEEI--P-PGGAVYITTEGSSGLASSYKT-----QDTI
 LGVVTADISLEWLRTFIKSISI--Y-QSGYAFLLSRNGVFLSHP-ND-----QFI
 IGVSVDVLSLAALADRLSAVKP--F-GSGRVYLLSQSGKWLAAHP-IP-----ELL
 WGVVTSDISLASLQKINQIKP--WEGGGYAMLLSSAGKVISYP-DK-----SQT
 AGIGGVDSLEYVDEVVSKVRT--F-DTGYAFMVNSGVILSHPHTHK-----DWI
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AM_Verrucomicrobiota_WP_129046516.1
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 PU_Firmicutes_R14_WP_021170906.1
 PU_Gproteobac_R4_WP_199478134.1

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 PU_Actinobacteriota_R8_WP_227113344.1
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 PU_Firmicutes_R15_WP_207952809.1
 PU_Firmicutes_R14_WP_021170906.1
 PU_Gproteobac_R4_WP_199478134.1

AGVVGV~~DL~~PLETLGAEIAKV~~V~~--G-ETGYAALVSNTGIYAAHP-RA-----ERL
 IGVAGI~~DL~~STDGIWSMLKT~~V~~KP--F-DSGSIHLISNDGVWAGHP-DS-----ERM
 VGVTVG~~DL~~SINYLQDMVVKANV--FDGHGNFDIVSHQGVFAANSNGNP-----DFV
 LGVVGA~~DL~~ISLDMVQVEKIRP---MGGYATMITAGDSYLANGFDR-----ALV
 YGVVGV~~DL~~IEVDFIKELVKGSEND-M-EFKDILIISSKGNIVGS--KY-----EMA
 RGAVGA~~DL~~SLAFIQDLLKRADQQLYDGAGEMALIASNGLRVAYTRDD-----SKL
 IGVAALGLSVNELADFI~~R~~KQKI--G-NSGFVYLVSPDGA~~F~~VIHR-DA-----ALA
 VGVAGMGLRMTELSKLIHDFS~~F~~--G-EHGKVFLVRNDGLIQVHP-DA-----AFS
 -GLAGLAKSLDSMVSMANFRI--G-DSGFVFM~~T~~DGSGKV~~L~~HP-DA-----ARI
 MGIIGVGLKVNSLQMLLKGYND--K-FDVVARLIDDKGFVQLAV-DK-----TGH
 LAIVGVGFRMDDLKELLAGFEA--R-TDTRVRL~~L~~ADDTIRAST-DP-----NEN
 LGAVGLGRSTS~~Q~~LT~~R~~RIQQAER--T-NGIQVMFLDGRGRILFSP-RR-----GQA
 IGVTGVGLPVQ~~R~~VTQLIET~~Y~~EQ--R-YNR~~T~~IY~~L~~IDEDGDV~~M~~LHS-KA-----FHR
 LGVIGVGLSSDAVSALVEKY~~Q~~K--R-YNRHIYF~~I~~NELGEV~~T~~LHG-SH-----
 IGATGVGLVTKVNR~~L~~ISRYEA--K-YDRQIYFVDASGNV~~V~~LRP-SN-----STM
 IGMTGVGLTVKNVNN~~L~~ISHYEA--K-YQRQIYFLNKDGEIV~~L~~RP-SN-----SPL
 IGAAGTGLTVNRVNALIEEYEG--R-FNREIFFVDREGNIILGP-SK-----GRL
 YGVAIGMNLDDIVNLVTSK~~T~~M--G-EGSKFLMVDS~~S~~GIVKIEK-----SDRV
 LGETGVGLSLKQSAEQFQ~~Q~~FKY--G-DKSHLWLVDREGTIY~~L~~SD-RY-----EQA
 VGVAGIGLSLKELANNFTN~~Y~~KY--G-ANSNVWLVDKSGKIY~~L~~SD-RV-----EDI
 VAVAGVALSLGDIAKEFGSYK~~F~~--G-EHSNLWLVDKQ~~G~~KIHLAD-DL-----EYN
 LVVAGLAIKV~~D~~KLIDMV~~K~~QLTI--G-KSGRAMLVTDQGV~~I~~QAKG-ESP-----AIDLI

MK-----TLSEVYPQNT-----PKIATG-----FSEAE~~L~~HGHTRIL
 GK-----TLTDIYPGAQ-----VSTG-A-----MQDVESADGARLL
 QQ-----DISKENIFKK-----MKGESG-----SMIEEFEGSRIV
 TK-----NISNKEWVKT-----ILSNEKG-----TDIHTWNEKVVI
 GK-----SVADMDWFKQ-----MINSKNKSG-----VIEYVYDGIK~~R~~MA
 NK-----LNIYKVP~~E~~LQE-----LA--AELKKGKQEG-----TVIYTFEGIRRIA
 GK-----NISKDQTLQT-----IASEKKG-I-----QDVNGKMV
 FK-----KLTESGIEAF-----RVLDKTD~~R~~CG-----SVSLEIKGKEWLA
 FK-----NVQ~~T~~MLGESS-----VEFMKEDHG-----IFTYGRNYC
 FE-----DIGTVLGEQA-----GFFLATEEG-----VLVHDGRYL
 FT-----NVS~~A~~VLGDDT-----DDFLGTEQG-----RIRLENDFF
 GT-----SLEEIDGYAEV-----ARGILGKGS~~G~~-ESGRQFSTTIAGRPHII
 MK-----ENITKPSGLIT-PELAEAG---RKMISGSPG---FVDYSEFQGBLRRT
 GQGWN---LQVDLVNLLHSEE-TQLQQLA---AEMIALNSG---CLRPLPLGDTVYVY
 LS-----DSLQSEADRTLTPELHAWV---TDIQNQAG---FQALTSYPDDRAHWL
 NP-----SIDHSPVLNA-----YKLNGDNN-----FFSYKLNNNEERLG
 -----NYSQLSDTWQKK~~T~~-----PDQRDRG-----YFSRDN~~S~~DMVFA
 KQ-----KGTDL~~L~~GSQA-----SRMEDDAAQ~~G~~-----LPRMTSGGQTVI
 GR-----VPSLSEVADPAL---RALI---GPDGQVRPG---TREFTVDRQAYS
 GMIIT---AAPS~~V~~SETEAAED-SVLIS---RIFQAWEKAG-----
 TRSEN---GLVSLPKAMQSRH-PLLRQSATALAQKTQDKKN-----SLALLIENKEIFV
 MR-----ESIFSLAETHSSKVL~~R~~DIG---KKMVQGETG---FVRLPEFVMGEPAWL
 MKEYDG-----EG-A-----
 SKAWQ-----GPTDNFTSS-----VVQHDDAILGEQALV
 GK-----KDLYDFGGEEL-----EKASRDIKNG-IGGHLETADPTTGKT~~V~~IL
 GK-----DLEETLVEQG-SRLQHID---EIKSAINSG-----EMYISTGKNFYT
 GK-----PMKDTDPWV~~V~~-----PFLGNLKKG-EAFETESFRTLN~~D~~MTYR
 GQ-----PIGKSDPALD-----AAKPAIRAG---RSFEQMSVADGQPVKQ
 GK-----NILEQKNIGAE-----DQLVDIEKG-----NSLTRIDNIGLK
 SKPYLPLPKGESLEELKEQAL-----TIMYTS~~D~~PM~~L~~GGTVMR
 YN-----QDENLKE-----EILHFKQG-----SHVEYSNGIFD
 GE-----
 DG-----QHFLRDTSGFNQ-----EMVTKLLMG--QRFSVSYSATDGERIA
 GK-----RQLAEQLGADA-----AKGVMTG-GESLRSSRFSRDGGERYLA
 DR-----DNLTQLASGTT-----ANLLTKQAF~~A~~-----ATQAEVDGQAVIL
 EN-----INFFENSSSDL-----SNSKQLILNNKKEQKSFWSSEKSKSYI
 GH-----ALFDTEEA~~A~~V-----LSEQTRSDRTDVQDFWYRANGENGFL
 PP-----QLQRAIAQQR-----LRDSLREQPRG-----AFQFRQGGELIYV
 AS-----NIHQQPG~~L~~QS-----LATQVLTS---PGGSYRYSNLNGENIFL
 -----HPGFDQIQREGLKT-----LATQILTS---PSVGASYADGQKVYL
 RG-----YDSLQEIEGLGE-----RVADLLAG---KTDSLTYKRLGDRRIM
 MN-----YQSLQNI~~P~~GLND-----VSTDLLAQ---ERTTLTYEREGTTYML
 TT-----YGNLDAV~~P~~GLKK-----DAQSLTSG--TEEQKIRYERD~~G~~KTYFL
 GK-----VNVKDV~~L~~GKEK-----FDVLMNKNKG-----VIRHFN~~G~~TRNLII
 GT-----KLNTILPGAV---SDEL~~F~~-----AGFANTQVVTYRTAQTGTIDL
 GA-----MISSFVPEEA---FEQML---GQLNETDSGLAKPVVLDYEDQEGKQMDL
 GR-----LAGDFLPAEV---MQQIL---GDM---DNATARPKVLEYQDSQGRIMDL
 KQ-----TDIASLLQDKN-----QVQIVERKISISGKDY~~Y~~L

AA_Proteobacteria_NP_252999.1	AFTPI-KGLPSVTWYLALSIDKDKAYAMLSKFRVSA-----
AA_Cyanobacteria_WP_162544314.1	GFQPI-AGLPGVDWYVAMSIDKGVAFELSDFRRLSTL-----
AA_Actinobacteriota_WP_187050447.1	GY----ATNPTTGWRIAGVMEENEVKVRASPM-----
AA_Bacteroidota_WP_196119247.1	SY----LTVPNTQWKLVGVNPN-IDKEVSPKKNRF-----
AA_Thermotogota_WP_114702178.1	GFSKM-----DNGWIFVTVALSKEVNKRATE-----
AA_Methanobacteriota_WP_056934003.1	GY----KRLSTTGWIVVATVP-----
AA_Firmicutes_NP_389278.2	VY----QTIGETGKWVGTDQDQDLMWISDKMNR-----
AA_Desulfobacterota_WP_144684422.1	EV----HTLPDLGWKLGVGFIERDEVMEGFRAMMRL-----
AA_Chloroflexota_WP_116224856.1	IY----YTSPLGWKIAAIIPI-----
AA_Halobacterota_WP_004039109.1	IY----ITSPELGWKIGTFIPVSTIEERINESIRQTL-----
AA_Thermoplasmata_OPX61375.1	VY----YTSTDMGWKIGTFIPNSYLASEIQES-----
AA_Spirochaetota_WP_018527208.1	RT----VTLENFGWHLAMAVP-----
AA_Singergistota_WP_012869308.1	FFSPT-----RSGFVLGVVFPASDLNAMVRS LAIRQ-----
AA_Verrucomicrobiota_WP_176014353.1	GY----APVASTDWSLAVVLP EADILKQSHCIEETIATESNRLEEEFQLSIHQ
AA_Planctomycetota_MBG80894.1	LY----EPVQEANWSMGTAIAEDDILAPVHQ-----
AA_Campylobacterota_WP_010891944.1	ACTKV-----FAYTACITESADIINKPIYKA-----
AA_Chrysiogenetota_WP_183731730.1	SS----TRIPSTQWQLVLFTRPDSFYAPIDPLRN-----
AA_Acidobacteriota_HCZ33114.1	GLSRTFSGPLGLHWKLLSVPE-----
AA_Deinococcota_WP_184108923.1	VVQPI-ALAPGVQWKGWGVYAPVDDFMLGLQRT-----
AA_Thermodesulfobacteria_RUM89741.1	-----MPLDSFVKVSMDSKWLASLRPLEQGDEA-----FYVG-----
AA_Fibrobacterota_WP_022637451.1	NSTP--FHKDNLHWNIVVAMPEAALMGDVRQQRNSR-----
AM_Desulfobacterota_WP_027185430.1	SY----APVNSDWSMGLVIPAEMFQGLEGLSRE-----
AM_Aproteobac_McpX_WP_014528895.1	-----
AM_Gproteobac_PacA_WP_039291840.1	TWQPVITIGNSTEKWYLG-----
AM_Halobacteriota_WP_011034866.1	FYEPV----ETGDFAFVLVVPKEMLAGVADLRER-----
AM_Spirochaetota_WP_015707342.1	VYMPIQFSSVTNPWSVAVSIPMAKILANADSIRNY-----
AM_Verrucomicrobiota_WP_129046516.1	FGVPVRIGSSSTPWCVSITIRESEVLGAWKLRNT-----
AM_Aproteobac_WP_041812266.1	LFLPVTVAGTETPWSLLVNLPLDKINAPVRELNRAT-----
AM_Bacteroidota_WP_092437134.1	AFVPVIVGRCPTAWQVSISVPVDYITQEARAQMIYQ-----
AM_Firmicutes_WP_056043800.1	LLNP--IHIKDQTYWFETIIPKGNMLKDYKGLSNT-----
AM_Firmicutes_WP_052635864.1	VYELINIRDIDDKWGKIKLSVDQKTIMGSASRLLANQ-----
AM_Gproteobac_PctD_WP_038403940.1	-----PAGSVL-----D-----
PU_Gproteobac_R3_WP_124259872.1	AA----SYVPELNLYIVAEPVQAEILGKITQT-----
PU_Gproteobac_McpH_WP_047603170.1	LG----LPLRDLNWTLVAEVPESEIYAQMHA-----
PU_Gproteobac_R1_WP_219614703.1	AT----SYIPMLDWYLVQAQVPEAEIYAELDKARLH-----
PU_Firmicutes_A_R5_WP_131005693.1	VC----QYIPSLKWHVLVLENDFTLMIKQLHLQ-----
PU_Actinobacteriota_R8_WP_227113344.1	VS----RYLPNLDWFLVVDHDTSQLDAQMARQ-----
PU_Cyanobacteria_R9_WP_198537540.1	RT----KRIPELNWTLVVSQPLRVPSGPLWS-----
PU_Gproteobac_R7_WP_038903150.1	NT----RVIPEFGWKLMVEQNSG-----
PU_Gproteobac_R6_WP_185834821.1	NS----RWVDEFQWYIIVEQKDE-----F-----
PU_Verrucomicrobiota_R10_WP_110129388.1	NC----RYVPELDWYLIVEQSEATMMAPLRQE-----
PU_Verrucomicrob_R11_WP_162024566.1	NC----RFIPELNWFLIIEQSEQELLAPIKEQ-----
PU_Verrucomicrobiota_R12_WP_220621668.1	NS----RWIPELNWYLMVEQSEDELLSPLRHTLL-----
PU_Campylobacterota_R2_WP_107944080.1	GS----KYIPSLDWYLFGEDEDVLLKDLHT-----
PU_Firmicutes_R13_WP_167859577.1	IS----RPIESADLDIVFAIPRSESVFPLHKIRTNT-----
PU_Firmicutes_R15_WP_207952809.1	IS----YPLKSTDWKLFLQMRSESVAFLDTIKLN-----
PU_Firmicutes_R14_WP_021170906.1	AY----QSTATTDWKLVFQIPRSESIAILSSVK-----
PU_Gproteobac_R4_WP_199478134.1	GA----LWVPMLDRFIVIEVPSEQILSPIYQQ-----

Figure S8. Inosine and theophylline do not alter colony morphology and c-di-GMP levels of *P. putida* containing the empty plasmid pBBR1MCS-2_START. **A.** Colony morphology and c-di-GMP levels (using c-di-GMP biosensor plasmid pCdrA::*gfp^C*) in the absence and presence of increasing inosine and theophylline concentrations. The brightness of the colony morphology images has been adjusted to optimize visibility. **B.** c-di-GMP synthesis during growth in liquid cultures of *P. putida* in the absence and presence of different theophylline concentrations. Experiments were conducted under identical condition as those shown in Fig. 7, except that the strain harbored the empty plasmid pBBR1MCS-2_START instead of the R6 expression plasmid pBBR1MCS-2_START_R6.

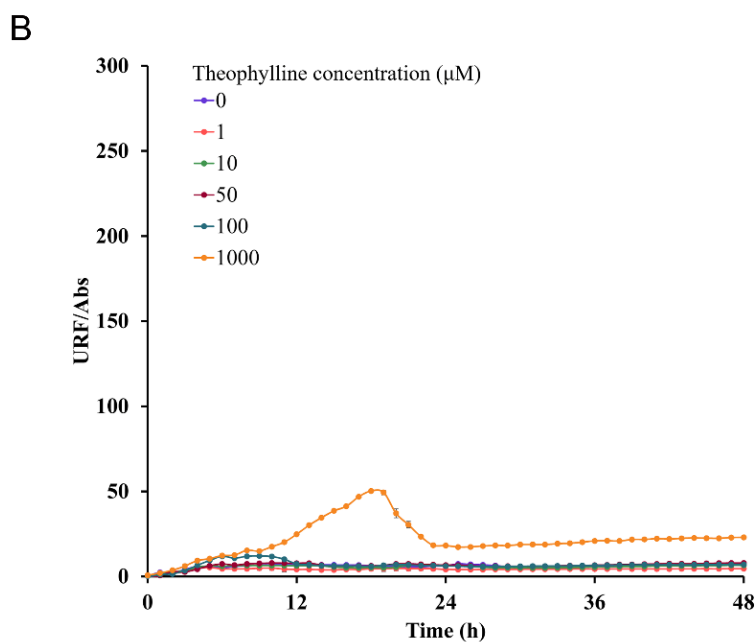
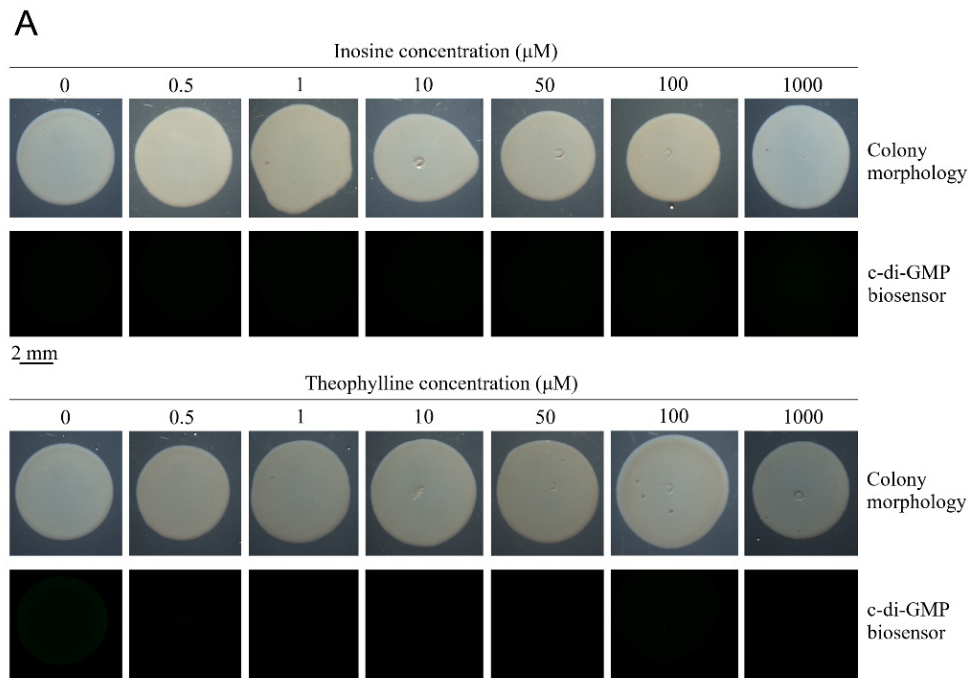


Table S1. Structural alignment of McpH-LBD with all structures deposited in the protein data bank using the DALI (3) algorithm.

PDB ID.	Acronym	Z-score	Rmsd ^a (Å)	Identity (%)	Species	Receptor family ^b	Bound ligand	Reference
3LIB	mmHK1S-Z3	19.1	2.9	15	<i>Methanosarcina mazei</i>	HK	-	(4)
7PRQ	PctD	18.8	3.0	16	<i>Pseudomonas aeruginosa</i>	CR	Choline	(5)
6MNI	PscC	18.6	3.1	16	<i>Pseudomonas syringae</i>	CR	Proline	(6)
5LT9	PctB	18.4	2.8	20	<i>P. aeruginosa</i>	CR	L-Arg	(7)
6FU4	TlpQ	18.3	3.2	17	<i>P. aeruginosa</i>	CR	Histamine	(8)
3LIF	rpHK1S-Z16	17.9	2.7	15	<i>Rhodopseudomonas palustris</i>	CR	-	(4)
6D8V	McpX	17.8	2.9	22	<i>Sinorhizobium meliloti</i>	CR	1,1-dimethyl-prolinium	(9)
6PZJ	-	17.7	3.0	14	<i>Leptospira interrogans</i>	CR	-	Unpublished
5ERE	-	17.2	2.9	11	<i>Desulfohalobium retbaense</i>	Stand-alone sensor domain	-	Unpublished
2ZBB	DctB	17.2	3.0	12	<i>Escherichia coli</i>	HK	Malonic acid	Unpublished
3BY9	DctB	17.2	3.3	13	<i>Vibrio cholerae</i>	HK	Succinic acid	(10)
3LIC	soHK1S-Z6	16.8	3.3	16	<i>Shewanella oneidensis</i>	HK	-	(4)
4WY9	Tlp1	16.1	3.1	12	<i>Campylobacter jejuni</i>	CR	-	(11)
6E0A	TlpA	16.0	3.1	12	<i>Helicobacter pylori</i>	CR	-	(12)
3LID	vpHK1S-Z8	15.7	3.8	12	<i>Vibrio parahaemolyticus</i>	HK	-	(4)
4XMQ	Tlp3 (CcmL)	15.0	3.2	13	<i>C. jejuni</i>	CR	-	(13)

^aRmsd, root mean square deviation

^bCR, chemoreceptor; HK, histidine kinase

Table S2. References for the lifestyle and pathogenicity of species harboring the 15 receptors studied (Table 2).

Name	Pathogenicity/characteristics	Refs.
R1	Fish pathogen, mainly salmon, important economic losses	(14)
R2	Human pathogen, causes inflammatory bowel disease	(15)
R3	Human pathogen, causes lung infections, high mortality rate	(16)
R4	Halophyte plant isolate, can promote plant growth	(17)
R5	Human pathogen, at times fatal, disrupts gut microbiota	(18)
R6	Human pathogen, causes life-threatening diarrheal disease	(19)
R7	Plant pathogen, in particular maize and rice	(20)
R8	Human pathogen, causes life-threatening bacteremia	(21)
R9	N ₂ -fixing bacterium, isolated from freshwater	(22)
R10	Isolated from a marine saltern	(23)
R11	Efficient degrader of fucoidan, a major algae product	(24)
R12	Isolated from deep sea cold seep	(25)
R13	N ₂ -fixing isolated from orchid roots	(26)
R14	Anaerobic, endospore forming bacterium, isolated from leafs	(27)
R15	Isolated from agricultural soil	(28)

Table S3. Presence of theophylline in different samples.

Sample type	Comment/reference
Plants and plant extracts	
Black tea	(29, 30)
Coffee	(31, 32)
Chocolate	(33)
Mate	(34)
Other plant products like lemon, pummelo or guaran	(35)
Bermuda grass	(36)
Citrus flowers (<i>Citrus limon</i> , <i>Citrus maxima</i> , <i>Citrus paradise</i>)	(37)
Different plants	(38)
Throughout the plant kingdom	(39)
Human/animals	
<i>Halotis discus hannai</i> (mollusc)	(40)
<i>Anopheles gambiae</i> (insect)	(41)
Human	Many different tissues, cells and excretions (35)
Mouse	ST000696 of https://www.metabolomicsworkbench.org
Rat	ST000017 of https://www.metabolomicsworkbench.org
Baboon	ST002132 of https://www.metabolomicsworkbench.org
Goat	ST001968 of https://www.metabolomicsworkbench.org
Squirrel	ST000724 of https://www.metabolomicsworkbench.org
Pigs	(42)
Microbiomes	
Nasal microbiome	(43)
Cervical microbiota	(44)
Gut microbiome of insects	(45)
Microorganisms	
<i>Escherichia soli</i>	(46)
<i>Staphylococcus aureus</i>	(47)
<i>Treponema pectinovorum</i>	Project ST000692 of https://www.metabolomicsworkbench.org
<i>Trypanosoma brucei</i>	(48)

Table S4. Strains and plasmids used.

Strains and plasmids	Genotype or relevant characteristics ^a	Ref.
Strains		
<i>Escherichia coli</i> BL21(DE3)	F ⁻ <i>ompT gal dcm lon hsdS_B(r_B⁻ m_B⁻)</i> λ(DE3 [<i>lacI lacUV5-T7p07 ind1 sam7 nin5</i>]) [<i>malB</i> ⁺] _{K-12} (λ ^S)	(49)
<i>Pseudomonas putida</i> KT2440	Wild type strain	(50)
Plasmids		
pET28_LBD_McpH	Km ^R ; pET28b(+) derivative containing the DNA fragment encoding McpH-LBD	(51)
pET28_LBD_McpH_Y121A	Km ^R ; pET28b(+) derivative containing the DNA fragment encoding McpH-LBD Y121A	This study ^a
pET28_LBD_McpH_R129A	Km ^R ; pET28b(+) derivative containing the DNA fragment encoding McpH-LBD R129A	This study ^a
pET28_LBD_McpH_W140A	Km ^R ; pET28b(+) derivative containing the DNA fragment encoding McpH-LBD W140A	This study ^a
pET28_LBD_McpH_F167A	Km ^R ; pET28b(+) derivative containing the DNA fragment encoding McpH-LBD F167A	This study ^a
pET28_LBD_McpH_D169A	Km ^R ; pET28b(+) derivative containing the DNA fragment encoding McpH-LBD D169A	This study ^a
pET28_LBD_McpH_D169N	Km ^R ; pET28b(+) derivative containing the DNA fragment encoding McpH-LBD D169N	This study ^a
pET28_WP_219614703-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_219614703-LBD (R1)	This study ^a
pET28_WP_107944080-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_107944080-LBD (R2)	This study ^a
pET28_WP_124259872-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_124259872-LBD (R3)	This study ^a
pET28_WP_199478134-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_199478134-LBD (R4)	This study ^a
pET28_WP_131005693-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_131005693-LBD (R5)	This study ^a
pET28_WP_185834821-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_185834821-LBD (R6)	This study ^a
pET28_WP_038903150-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_038903150-LBD (R7)	This study ^a
pET28_WP_227113344-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_227113344-LBD (R8)	This study ^a
pET28_WP_198537540-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_198537540-LBD (R9)	This study ^a
pET28_WP_110129388-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_110129388-LBD (R10)	This study ^a
pET28_WP_167859577-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_167859577-LBD (R13)	This study ^a
pET28_WP_021170906-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_021170906-LBD (R14)	This study ^a
pET28_WP_162024566-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_162024566-LBD (R11)	This study ^a
pET28_WP_207952809-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_207952809-LBD (R15)	This study ^a

pET28_WP_220621668-LBD	Km ^R ; pET28b(+) derivative containing a DNA fragment encoding WP_220621668-LBD (R12)	This study ^a
pBBR1MCS-2_START	Km ^R ; <i>oriRK2 mobRK2 lacZ</i>	(52)
pBBR1MCS-2_START_R6	Km ^R ; pBBR1MCS-2_START derivative containing full length coding sequence for WP_185834821 (R6) cloned into NdeI/BamH sites	This study ^a
pCdrA:: <i>gfp</i> ^C	Ap ^R , Gm ^R ; FleQ dependent c-di-GMP biosensor	(53)

Ap, ampicillin; Km, kanamycin; Gm, gentamicin.

^aGene synthesis and plasmid construction were done by GenScript Inc.

Table S5. Buffers used for the analysis of the recombinant proteins used in this study. Buffers were chosen to optimize protein solubility.

Protein name	Analysis buffer
McpH-LBD	3 mM Tris, 3 mM PIPES, 3 mM MES, pH 6.0
McpH-LBD Y121A	3 mM Tris, 3 mM PIPES, 3 mM MES, pH 6.0
McpH-LBD R129A	3 mM Tris, 3 mM PIPES, 3 mM MES, pH 6.0
McpH-LBD W140A	3 mM Tris, 3 mM PIPES, 3 mM MES, pH 6.0
McpH-LBD F167A	3 mM Tris, 3 mM PIPES, 3 mM MES, pH 6.0
McpH-LBD D169A	3 mM Tris, 3 mM PIPES, 3 mM MES, pH 6.0
McpH-LBD D169N	3 mM Tris, 3 mM PIPES, 3 mM MES, pH 6.0
WP_219614703-LBD (R1)	3 mM Tris, 3 mM PIPES, 3 mM MES, 150 mM NaCl, 10 % (v/v) glycerol, pH 7.0
WP_107944080-LBD (R2)	3 mM Tris, 3 mM PIPES, 3 mM MES, 150 mM NaCl, 10 % (v/v) glycerol, pH 8.0
WP_124259872-LBD (R3)	Insoluble
WP_199478134-LBD (R4)	3 mM Tris, 3 mM PIPES, 3 mM MES, 150 mM NaCl, 10 % (v/v) glycerol, pH 8.0
WP_131005693-LBD (R5)	3 mM Tris, 3 mM PIPES, 3 mM MES, 150 mM NaCl, 10 % (v/v) glycerol, pH 7.0
WP_185834821-LBD (R6)	3 mM Tris, 3 mM PIPES, 3 mM MES, 150 mM NaCl, 10 % (v/v) glycerol, pH 8.0
WP_038903150-LBD (R7)	Insoluble
WP_227113344-LBD (R8)	3 mM Tris, 3 mM PIPES, 3 mM MES, 150 mM NaCl, 10 % (v/v) glycerol, 1 mM β -mercaptoethanol, pH 6.0
WP_198537540-LBD (R9)	Insufficient protein expression
WP_110129388-LBD (R10)	3 mM Tris, 3 mM PIPES, 3 mM MES, 150 mM NaCl, 10 % (v/v) glycerol, 1 mM β -mercaptoethanol, pH 7.0
WP_162024566-LBD (R11)	3 mM Tris, 3 mM PIPES, 3 mM MES, 150 mM NaCl, 10 % (v/v) glycerol, 1 mM β -mercaptoethanol, pH 7.0
WP_220621668-LBD (R12)	3 mM Tris, 3 mM PIPES, 3 mM MES, 150 mM NaCl, 10 % (v/v) glycerol, pH 7.5
WP_167859577-LBD (R13)	3 mM Tris, 3 mM PIPES, 3 mM MES, 150 mM NaCl, 10 % (v/v) glycerol, pH 7.0
WP_021170906-LBD (R14)	Unfolded protein
WP_207952809-LBD (R15)	3 mM Tris, 3 mM PIPES, 3 mM MES, 150 mM NaCl, 10 % (v/v) glycerol, pH 7.0

Table S6. Sequences of recombinant proteins used in this study. The hexa-histidine containing extension and mutations to alanine or asparagine are shown in bold face.

Protein name	Protein sequence (including his-tag)
McpH-LBD	MGSSHHHHHHSSGLVPRGSHM NRLTDRYLVDLTALPASIEAIRNDIERMLG QPLVAAADIAGNTLLRDWLAAGEDPAQAPQFIEYLTAAKQRNHAFTTLFA STETGHYYNENGLDRTLRSRNPDKWFGYIDSGAERFINIDIDGATGEL ALFIDYRVEKEGKLVGVAGMGLRMTELSKLIHDFSFGHEGKVFLVRNDGL IQVHPDAAFSGKRQLAEQLGADAAKGVMGTGGESLRSSRFSRDGERYLALG LPLRDLNWTLLVAEVPESIEIYAQM HQ
McpH-LBD Y121A	MGSSHHHHHHSSGLVPRGSHM NRLTDRYLVDLTALPASIEAIRNDIERMLG QPLVAAADIAGNTLLRDWLAAGEDPAQAPQFIEYLTAAKQRNHAFTTLFA STETGH A YNENGLDRTLRSRNPDKWFGYIDSGAERFINIDIDGATGEL ALFIDYRVEKEGKLVGVAGMGLRMTELSKLIHDFSFGHEGKVFLVRNDGL IQVHPDAAFSGKRQLAEQLGADAAKGVMGTGGESLRSSRFSRDGERYLALG LPLRDLNWTLLVAEVPESIEIYAQM HQ
McpH-LBD R129A	MGSSHHHHHHSSGLVPRGSHM NRLTDRYLVDLTALPASIEAIRNDIERMLG QPLVAAADIAGNTLLRDWLAAGEDPAQAPQFIEYLTAAKQRNHAFTTLFA STETGHYYNENGLD A TLSRNPDKWFGYIDSGAERFINIDIDGATGEL ALFIDYRVEKEGKLVGVAGMGLRMTELSKLIHDFSFGHEGKVFLVRNDGL IQVHPDAAFSGKRQLAEQLGADAAKGVMGTGGESLRSSRFSRDGERYLALG LPLRDLNWTLLVAEVPESIEIYAQM HQ
McpH-LBD W140A	MGSSHHHHHHSSGLVPRGSHM NRLTDRYLVDLTALPASIEAIRNDIERMLG QPLVAAADIAGNTLLRDWLAAGEDPAQAPQFIEYLTAAKQRNHAFTTLFA STETGHYYNENGLDRTLRSRNPDK A FGYIDSGAERFINIDIDGATGEL ALFIDYRVEKEGKLVGVAGMGLRMTELSKLIHDFSFGHEGKVFLVRNDGL IQVHPDAAFSGKRQLAEQLGADAAKGVMGTGGESLRSSRFSRDGERYLALG LPLRDLNWTLLVAEVPESIEIYAQM HQ
McpH-LBD F167A	MGSSHHHHHHSSGLVPRGSHM NRLTDRYLVDLTALPASIEAIRNDIERMLG QPLVAAADIAGNTLLRDWLAAGEDPAQAPQFIEYLTAAKQRNHAFTTLFA STETGHYYNENGLDRTLRSRNPDKWFGYIDSGAERFINIDIDGATGEL AL A IDYRVEKEGKLVGVAGMGLRMTELSKLIHDFSFGHEGKVFLVRNDGL IQVHPDAAFSGKRQLAEQLGADAAKGVMGTGGESLRSSRFSRDGERYLALG LPLRDLNWTLLVAEVPESIEIYAQM HQ
McpH-LBD D169A	MGSSHHHHHHSSGLVPRGSHM NRLTDRYLVDLTALPASIEAIRNDIERMLG QPLVAAADIAGNTLLRDWLAAGEDPAQAPQFIEYLTAAKQRNHAFTTLFA STETGHYYNENGLDRTLRSRNPDKWFGYIDSGAERFINIDIDGATGEL ALF I A YRVEKEGKLVGVAGMGLRMTELSKLIHDFSFGHEGKVFLVRNDGL IQVHPDAAFSGKRQLAEQLGADAAKGVMGTGGESLRSSRFSRDGERYLALG LPLRDLNWTLLVAEVPESIEIYAQM HQ
McpH-LBD D169N	MGSSHHHHHHSSGLVPRGSHM NRLTDRYLVDLTALPASIEAIRNDIERMLG QPLVAAADIAGNTLLRDWLAAGEDPAQAPQFIEYLTAAKQRNHAFTTLFA STETGHYYNENGLDRTLRSRNPDKWFGYIDSGAERFINIDIDGATGEL ALF I N YRVEKEGKLVGVAGMGLRMTELSKLIHDFSFGHEGKVFLVRNDGL IQVHPDAAFSGKRQLAEQLGADAAKGVMGTGGESLRSSRFSRDGERYLALG LPLRDLNWTLLVAEVPESIEIYAQM HQ
WP_219614703-LBD (R1)	MGSSHHHHHHSSGLVPRGSHM QRSAQQLIETRMFEQELPNLTQRIKKEIE KDLTSVANAARQLANDRFVLDWVARGMPKEQESILIDQLKDMTAQYGLVT ASFADRQSAAYYNQDGFRLNLTPEQDAWFYGYTKSPQDMLLSIFRETNGE VKLFVNFQQNLNGRGLAGLAKSLDSMVSMLANFRIGDSGFVMTDGSQKVK LHPDAAARIDRDNLTQLASGTTANLLTKQAFATQAEVDGQAVILATSYP MLDWYLVAQVPEAEIYAELDKARLH
WP_107944080-LBD (R2)	MGSSHHHHHHSSGLVPRGSHM NLYTEKVVKDELPLAVSNVAGEIGYAIK IINTSYQMTKNDYLLKWIDEGEPKDGATLTFNYNTDLMKAFNLSTAMFVS DKTLNYYTNDKILKQLSKDNPRDSWYFDVKNGKEVNSLNIQVSEATGSLT

	LYVNSKVEKDGTKFYGVSAIGMNLDDIVNLVTSKTMGEGSKFLMVDSSGIV KIEKSDRVGKVNVDVLGKEKFDVLMNKNGGVIRHFNGTRNLIIGSKYIP SLDWYLFGEDEVDLLKDLHT
WP_124259872-LBD (R3)	MGSSHHHHHHSSGLVPRGSHM KERAREQDLPTALGEIRSEVLRQIAAPVA LTRSLATNEYIILNWEEQGLPEQGAAAWKTYAQTLKNESHAATIAWVSEKT GKYLDENGFSRTVQSRDATDNWFYDFLSKKGQLEIKLGKDKASSVYNLFI DARFDVNGKIGVAALGLSVNELADFIKQKIGNSGFVYLVSPDGAFVIHR DAALADGQHFLRDTSGFNQEMVTKLLMGQRFSSVSYSATDGERIAAASYV PELNLYIVA EVPQAEILGKITQT
WP_199478134-LBD (R4)	MGSSHHHHHHSSGLVPRGSHM MESDLKQLKEELLPNRLHSLSSRISEQIS PLINASKLMTNDRFIADWVKKGADSRPLVAEELNSIKQLSGSDSTFYV VNMKSGLEFLGYDQKFFRTPLADYPYKEFYPNFLAKNKDYELNLQYADQK LYINYRSREMDPTTGKPLVAVGLAIKVDKLIDMVKQLTIGKSGRAMLVTD QGVIAQAKGESPAIDLIKQTDIASLLQDKNQVQIVEKSISGKDYYLGALWV PMLDRFIVIEVPSEQILSPIYQQ
WP_131005693-LBD (R5)	MGSSHHHHHHSSGLVPRGSHM GYQSN TNIFKNDIEHVSTLAAEGIYYQID KLLSEPINVSLTMANDSLLKNFLDGEKEHLNDEEFIYKLQDYLN VYRNKY SYDSVFLVSTKTNNYYHFNGLDNRNLSANNSENQWYTF LKNDD EYSLNVD NDEASNNSITVFNCKIKDDNGATMGIIGVGLKVNLSQMLLKGYNDKFDV VARLIDDKGFVQLAVDKTGHENINFFENSSSDLSNSKQLILNNKKEQKSF WYSSEKSKSYIVCQYIPSLKWHLVLENDFTLMIKQLHLQ
WP_185834821-LBD (R6)	MGSSHHHHHHSSGLVPRGSHM HDTLEEQINKDSLPLTSDNIYSEIQQDLI RPIFISSLM AQDTFVREWTLAGEQDPERIIRYLREIQRQYQTISSFYISD RTGHYYHYTGILKQVSESNPNDAWFYRVKNSAPDKNFVNIDIDTANSQQ TVVFVNYKVDFDFENRFLGVIGVGLSSDAVSALVEKYQKRYNRHIYF INEL GEVTLHGSHHPGFDQIQQREGLKTLATQILTSPSVGASYADGQKVYLS RWVDEFQWYIIVEQKDEFNHD
WP_038903150-LBD (R7)	MGSSHHHHHHSSGLVPRGSHM ARHS LFDEISESSLPLTSDNVYSEIQRDL LNPIFISSLM AHDTFVKDWVLSNETDPQAMTRYLREIDRRFNTVVSFFVS NNTHRYDPEKISHTLLETSPEDKWFFDIRDEKDGDPYDIEIGVDPENRT RMDIFIN YKVFDYSGNFIGVTGVGLPVQRVTQLIETYEQRYNRTIYLIDE DGDVMLHSAFHRASNIHQQPGLQSLATQVLTSPGGSYRYS LNGENIFLN TRVIPEFGWKLMVEQNSGPHDRQLWLTL LKN
WP_227113344-LBD (R8)	MGSSHHHHHHSSGLVPRGSHM GYQSSRAAFEKDAERTSLAAEGAAREID NRFAEPIDVSLAMAHDTLLADLLSAEPTRGDDEAYADAVCAYLESYREAF GFDSVFLVSTESNRYYHFNGVDRTLERNPENTWYFDFLDRDEAYS LNVD NDEATADEITMFVNARILDEQGSTLAIVGVGFRMDDLKELLAGFEARTDT RVRL LADDGTIRASTDPNENGHALFDTEEA AVLSEQTRSDRTDVQDFWYR ANGENGFLVSRYLPNL DWFLVVDHDTSQLDAQMARQF
WP_198537540-LBD (R9)	MGSSHHHHHHSSGLVPRGSHM ANALAAARRQVVESTLPLTL DAL SADLQQ DFVQPILFASAMAANTLLIDWVEQGEQPEAAVQRYLSRVQAQHGATTVFF VSEASRRYYHPTGILKTVSPGSAQDAWFFRLRASASSYEVNLD RDTADPS RTTVFVNYKLLGDGGRFLGAVGLGRSTS QLTRRIQQAERTNGIQVMFLDG RGRILFSPRRGQAPPQLQRAIAQQRLRDSLREQPRGAFQFRQGGELIYVR TKRIPELNWTLVVSQPLRVPSGPLWS
WP_110129388-LBD (R10)	MGSSHHHHHHSSGLVPRGSHM VSRRNNVRKTLAESTLPLTSDNVYSEIQRD LLRPVFIASLMANDTFLRDWAIAGEKDRDAIVRYLHEIKIKYGTVSSFFV SDKTLKYYYAHGLLKT VSEDEPRDEWYFRVREMDEPYEINVD PDMANQDA LTIFIN YRVRDYAGNFIGATGVGLTVTKVNRLISRYEAKYDRQIYFVDAS GNVVL RPSNSTMRGYDSLQEI EGLGERVADLLAGKTD SLTYKRLGDRRIM NCRYVPELDWYLIIVEQSEATMMAPLRQE
WP_162024566-LBD (R11)	MGSSHHHHHHSSGLVPRGSHM RSNMRLSITESTLPLTSDNVYSEIQRDLL RPIFISSLMANDTFLRDWALNGEVDINQITKFLHEIKVEYSTISSFFVSD ISHNYYHAQGLLKEVKENEPRDAWYFKARDMDAPYEINVD LDMANQDQMT IFIN YRVFDYNDNFIMGTVGLTVKNVNNLISHYEAKYQRQIYFLNKDGE

	IVLRPSNSPLMNYQSLQNIPLGNDVSTDLLAQERTTLTYEREGTTYMLNCRFIPELNWFLLIEQSEQELLAPIKEQ
WP_220621668-LBD (R12)	MGSSHHHHHHSSGLVPRGSHM SLPLTADNIYSVIQRDLLRPIFISSMMAN DAFLRDWTINGEVDVKQMQRYLEEIRREYGTVTSTFFISEKSRNYYYWGGV LKQVDENEPRDVWYFRVREMEKPFIEINVDIDMANNDALTVFVNRYRVDYE GNYIGAAGTGTLVNRVNALIEEYEGRFNREIFFVDREGNIILGPSKGRLT TYGNLDAVPGLKKDAQSLTSGTEEQKIRYERDGTKYFLNSRWIPELNWYL MV
WP_167859577-LBD (R13)	MGSSHHHHHHSSGLVPRGSHM TQREAVDKLKTCDLLHLADSIAAKVDGQI RKAKETSLLMAEDPNVINWVAGGERDEALGAVVGRKLTLLTSEHGYDNSF LVSAVSNNRYWEGGTVLRTMSRSDPEDAWFYANVDNRKPIEIVLDYAIAR GDTFVFNALIGGAERALGETGVGLSLKQSAEQFQQFKYGDKSHLWLVD EGTIYLSDRYEQAGTKLNTILPGAVSDELFAGFANTQVVITYRTAQTGTID LISRPIESADLDIVFAIPRSESVPFLHKIRTNT
WP_021170906-LBD (R14)	MGSSHHHHHHSSGLVPRGSHM THNAMVDKLNKRDMLYIVQSMSEKIDGRI ERAQETSLLLADDPTVLAWVESGGRDEAAGEIVKTKITDIGKNYDYVKAF VASTVTNQYWEDNKVVKPLSKTSYTDKWFYKALKSGKKIELNIDYDSIHN ETFIFFNTLVGDVVRQPVAVAGVALSLGDIAKEFGSYKFGEHSNLWLVDKQ GKIHLADDLEYNGRLAGDFLPAEVMQQILGDMDNATARPVKVLEYQDSQGR IMDLAYQSTATTDWKLVFQIPRSESIAILSSVK
WP_207952809-LBD (R15)	MGSSHHHHHHSSGLVPRGSHM EKEVVNKLKSKDLVRIAESIASKIDGRLQ RAQESSLTAMDPELIEWLASGEKDQIAGAHVLQKLDNLAKGFDYSNGFI ASRMTGSYWIEGKQMSKILSQTNPADKWFYDSFASQKRMALNIDYNSRR DTFVFNVLVGDVESPVGVAGIGLSLKELANNFNTNYKYGANSNVWLVDKS GKIYLSDRVEDIGAMISSFVPEEAFEQMLGQLNETDSGLAKPVLVDYEDQ EGKQMDLISYPLKSTDWKLFLQMRRESVAFLDTIKLN

Table S7. Data collection and refinement statistics. Statistics for the highest-resolution shell are shown in parentheses.

Ligand	Uric Acid
PDB ID	8BMV
Beam Line	XALOC (ALBA)
Space group	P 1 21 1
Unit cell a, b, c (Å)	32.581 124.322 57.201
Resolution (Å)	32.15 - 1.95 (2.02 - 1.95)
Unique reflections	31376 (3258)
Multiplicity	2.9 (3.1)
Completeness (%)	96.01 (99.48)
I/ σ I	13.07 (1.73)
Wilson B-factor	36.6
R _{merge} (%)	5.17 (70.7)
CC(1/2)	0.998 (0.678)
CC	1 (0.899)
Refinement	
R _{work} /R _{free} (%)	18.27 / 23.12
CC _{work} /CC _{free}	0.97 / 0.91
No. atoms	4177
Protein	4037
Ligands	24
Solvent	116
B-factor (Å ²)	47.50
R.m.s deviations	
Bond lengths (Å)	0.009
Bond angles (°)	1.01
Ramachandran (%)	
Favoured (%)	97.55
Outliers (%)	0.00

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