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A tandem and tunable Pd catalyzed C–N coupling of heteroarenols with ureas via C–OH bond activation

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ABSTRACT

At this circumstance for the first time, a facile and convenient method for heteroaryl ureas has been developed via a two-step process involving in situ C–OH activation followed by palladium catalyzed C–N coupling of heteroarenols with ureas, which show excellent functional group tolerance and give out rapid coupling in good to excellent yield.

1. Introduction

Pd-catalyzed cross-coupling reactions have qualified to being the mainly consistent and prominent methodology for the creation of C–N bond.[1] The easy-going reaction condition, outstanding functional group tolerance, and the quick synthesis continue this reaction to being mandatory tools in organic chemistry.[2] Numerous efforts have also been framed to make the cross-coupling reactions further relevant since the advance of this reaction. The pre-activated substrates such as pseudo halides have to be most usually consumed in this cross-coupling reaction. In the focus of scrutiny to heteroaryl halides are typically prepared from simply accessible heteroarenols. These transformations to heteroaryl halides can be precious, often require harsh condition, toxic reagents, and multistep syntheses. Annihilation of functionality or loss of protecting group may be caused underneath these circumstances.[3] As a result, straight C–OH bond activation of heteroarenols for cross-coupling reaction is significantly preferred and receive enormous attention in organic synthesis.[4] The relevance of C–OH bond containing compounds as electrophiles in cross coupling reaction experience major defies like requirement of high bond dissociation energy of inert C–OH bond and thermodynamically dispute to cleavage inert C–OH bond. So, we have held core on the affecting heteroarenols possess active C–OH bond.

N-heteroaryl substituted ureas have drawn immense consideration for the design of biologically relevant molecules with extensive biomedical appeal as therapeutics and are normally originated as a functional moiety in natural product. According to reported survey, *N*-heteroaryl urea seems to be crucial for biologically potency in drugs (Fig. 1).[5] They have assembled enormous planning among chemists due to their wide array of biological activities. The classical methods for the synthesis of *N*-heteroaryl substituted ureas were prepared by the reaction of heteroaryl amines with isocyanates.[5,6] As common and conventional alternate route of synthesis are of condensation of heteroaryl amines with carbamates.[7] In this context, heteroaryl amines are prepared by amination reaction of hetero aryl chloride. In such cases, aminolysis reactions are carried out under the typical conditions concern of ammonium hydroxide (or ammonia), high temperature and pressure, lengthened periods of time and sealed reactor etc., thus creating a prospective safety risk and also yielding at law quantity and purity. Furthermore, both isocyantates and carbamates are highly toxic, unstable, and typically require the make use of phosgene for their synthesis.[8] So, we have chosen the new and alternate way of synthesis of *N*-heteroaryl urea derivatives by way of Palladium catalyzed C–N couplings of heteroarenols with a variety of urea via in situ C–OH bond activation.

As to the catalytic reaction of arylation of ureas, this is of substantial value for organic synthesis. In this fact, central progress of Pd-catalyzed reaction has arisen for *N*-arylation of urea.[9] These intact reported outcomes impelled us to explore the application of the Pd-catalyzed C–N coupling reaction of heteroarenols with

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0040-4020/

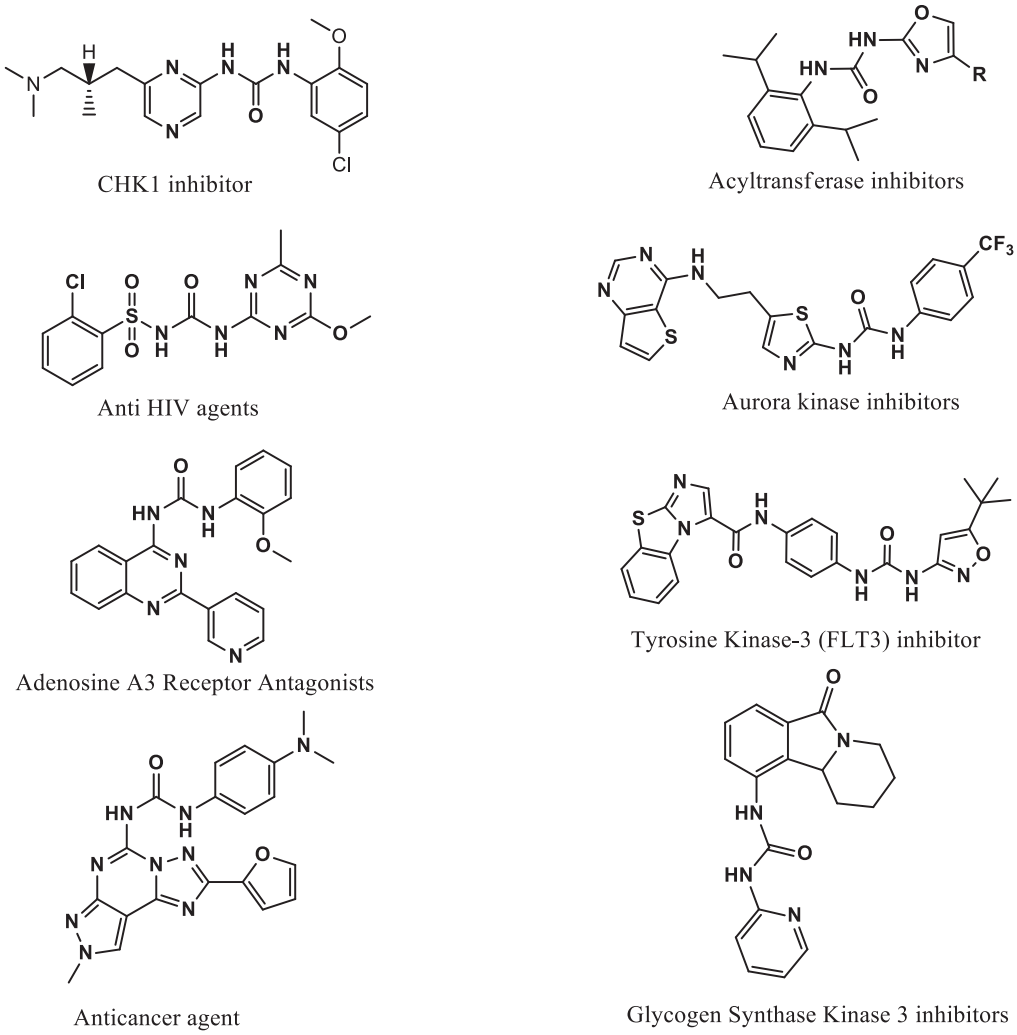


Fig. 1. Urea based biological potential compounds.

different type of urea as coupling partners. However, to the best of our knowledge, Palladium catalyzed C–N coupling reaction via in situ C–OH bond activation between heteroarenols with weak nucleophilic coupling partners various type of ureas has never been reported.

In this article, we report a method for synthesis of N-heteroaryl substituted urea derivatives via Pd-catalyzed C–N coupling reaction of heteroarenols with ureas through in situ C–OH bond activation.

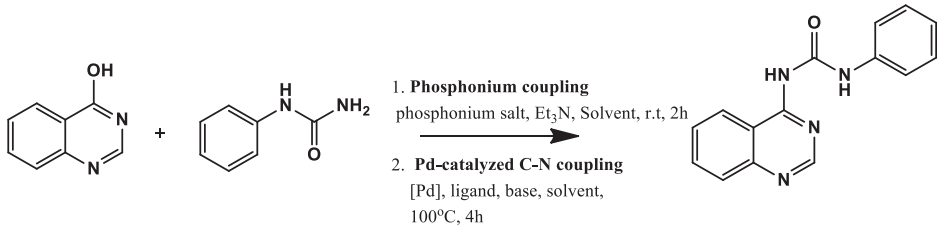
2. Result and discussion

In our preface exploration of a range conditions for direct synthesis of *N*-substituted the model substrates. 4-quinazolinone was first activated in situ with phosphonium reagent and then development of condition for Pd-catalyzed C–N cross coupling were explored. These were the essentially assortment of C–OH bond activation by phosphonium coupling and subsequent Pd-catalyzed C–N coupling with urea in one pot synthesis. We predicted that underneath Pd heteroaryl urea derivatives, 4-quinazolinone and phenyl urea were initially designated as the model substrates. As catalyzed cross-coupling condition; the resultant heterocycles-phoshphonium salt might chemically perform similar to some of the known preactivated oxygen containing cross-coupling allies, such as sulfonates. This would undertake Pd-catalyzed direct *N*-heteroarylation of the ureas to afford the *N*-substituted heteroaryl ureas with new C–N bond formation. To the beginning of the intensive study, we preliminarily examined this type of tandem reaction of 4-quinazolinone with phenyl urea by the using a combination of phosphonium coupling and Pd-catalyzed C–N cross coupling. The C–OH bond of 4-quinazolinone were activated in the presence of phosphonium reagent, base, and solvent at rt for 2 h. Then Pd catalyst, ligand, and phenyl urea were introduced and the mixture was stirred at 100 °C for 4 h. A series of phosphonium reagents, bases, solvents, Palladium sources, and ligands were screened for the feasibility of approach for a merger of both couplings.

The results of the reaction optimization are summarized in Table 1. The coupling reactions were practically examined with appearance and the disappearance of the active alkoxy phosphonium salt. The highest yield was achieved by utilizing two standard conditions: the phosphonium coupling condition (PyBroP, Et_3N, 1,4-dioxane) and the Pd-catalyzed C–N coupling condition ($Pd_2(dba)_3$, Ligand **L**, (Fig. 2) Cs_2CO_3, 1,4-dioxane) (Table 1, Entry 8).

In favor of assessment aim, familiar phosphonium salts were examined for phosphonium Coupling. Among them, the Br-derived reagents (PyBroP and BroP) were extreme more effectual than the OBt-derived reagents (PyBOP, BOP, PyAOP) and other reagent HATU possibly because the concluding simultaneously generated the heterocycle-OBt ether as the side product, that almost close up the cross-coupling reaction. PyBroP was accredited as outstanding for

Table 1
Reaction optimization[a]



(IIA) (IIB) (II)

Phosphonium coupling				Pd catalyzed C–N coupling				
Entry	Phosphonium salt	Base	Solvent	Catalyst	Ligand	Base	Solvent	Yied %
1	PyBroP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Xphos	Cs_2CO_3	1,4-dioxane	53
2	PyBroP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Brettphos	Cs_2CO_3	1,4-dioxane	56
3	PyBroP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Dppf	Cs_2CO_3	1,4-dioxane	40
4	PyBroP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Josiphos	Cs_2CO_3	1,4-dioxane	43
5	PyBroP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	DPEphos	Cs_2CO_3	1,4-dioxane	38
6	PyBroP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	1,4-dioxane	59
7	PyBroP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	BINAP	Cs_2CO_3	1,4-dioxane	35
8	PyBroP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Ligand	Cs_2CO_3	1,4-dioxane	89
8[a]	PyBroP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Ligand	Cs_2CO_3	1,4-dioxane, H_2O	97
9	BOP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Ligand	Cs_2CO_3	1,4-dioxane	37
10	BrOP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Ligand	Cs_2CO_3	1,4-dioxane	59
11	PyBOP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Ligand	Cs_2CO_3	1,4-dioxane	42
12	PyAOP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Ligand	Cs_2CO_3	1,4-dioxane	39
13	HATU	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Ligand	Cs_2CO_3	1,4-dioxane	34
14	PyBroP	Et_3N	1,4-dioxane	$Pd(OAC)_2$	Ligand	Cs_2CO_3	1,4-dioxane	60
15	PyBroP	Et_3N	1,4-dioxane	$Pd(dppf)Cl_2$	Ligand	Cs_2CO_3	1,4-dioxane	54
16	PyBroP	Et_3N	1,4-dioxane	$Pd(Ph_3P)_2Cl_2$	Ligand	Cs_2CO_3	1,4-dioxane	50
17	PyBroP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Ligand	NaO*t*Bu	1,4-dioxane	46
18	PyBroP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Ligand	K_3PO_4	1,4-dioxane	39
19	PyBroP	Et_3N	1,4-dioxane	$Pd_2(dba)_3$	Ligand	K_2CO_3	1,4-dioxane	33
20	PyBroP	Et_3N	THF	$Pd_2(dba)_3$	Ligand	Cs_2CO_3	THF	62
21	PyBroP	Et_3N	Toluene	$Pd_2(dba)_3$	Ligand	Cs_2CO_3	Toluene	77
22	PyBroP	Et_3N	DMF	$Pd_2(dba)_3$	Ligand	Cs_2CO_3	DMF	41
23	PyBroP	Et_3N	*t*-BuOH	$Pd_2(dba)_3$	Ligand	CS_2CO_3	*t*-BuOH	33

1. *Phosphonium coupling*: 4-quinazolinone (1 mmol), Phosphonium salt (1.50 mmol), triethyl amine (2.0 mmol), solvent (5.0 mL), rt, 2 h. 2. *Pd catalyzed C–N coupling*: Pd: 1.6 mol %, ligand: 5 mol %, base: 1.4 mmol, 100 °C, 4 h.
[a] 1,4-dioxane+H_2O was used as 5:1 ratio. Water was added at Pd catalyzed C–N coupling condition.

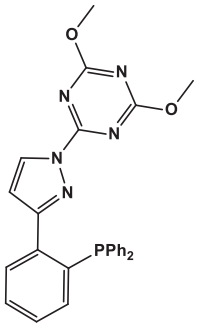


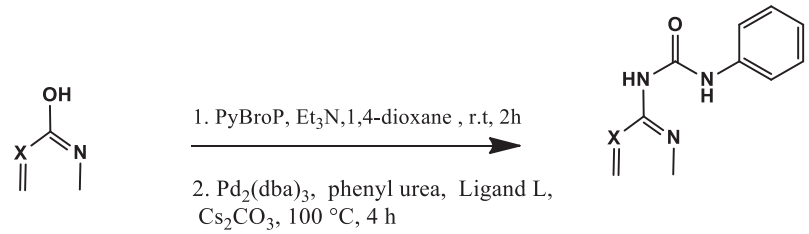
Fig. 2. Ligand L (2-(3-(2-(diphenylphosphino)phenyl)-1*H*-pyrazol-1-yl)-4,6-dimethoxy-1,3,5-triazine).

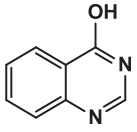
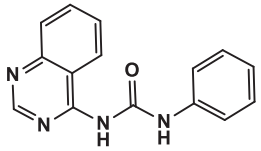
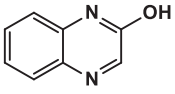
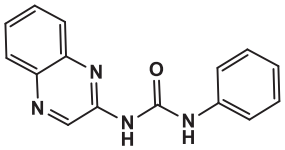
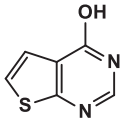
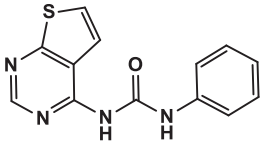
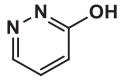
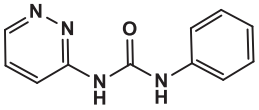
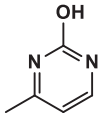
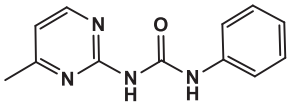
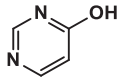
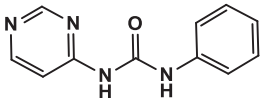
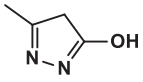
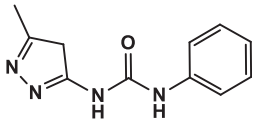
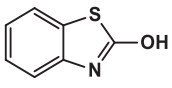
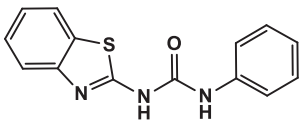
the phosphonium coupling. In the next phase, regarding the Pd source was also tested. Other Pd-catalyst provided less effective catalyst system than $Pd_2(dba)_3$. With $Pd_2(dba)_3$ as the best reagent of choice for Pd catalyzed C–N coupling. The outcome of different bases on the reaction was inspected for viability of Pd catalyzed C–N coupling approach. The highest yield was accomplished by making use of Cs_2CO_3. In addition, different solvent systems were also screened. 1,4-dioxane afford in highest yield contrast to other solvent. The Pd-catalyzed C–N coupling reaction appeared to be vigorous in presence of water. The presence of water was found to have a significant impact on the conversion of some Buchwald-Hartwig reactions as per previous report.[10]

About recognized the optimistic screening outcome; concentration was curved to establish the extent and the generalization of the process. We embarked on an exploration of the reaction scope by varying heteroarenols for Pd catalyzed C–N coupling with ureas by operating a feasible catalyst system based on optimized condition via in situ C–OH bond activation using PyBrop.The obtained results resumed in Table 2 reveal that the optimized conditions proved to be generalize for the coupling of phenyl urea with a range of these heteroarenols. Complete conversion and good to excellent isolated yields were observed for all the heteroarenols employed.

Next, the prospect of variation in ureas including aromatic ureas, benzylic urea, urea, and cyclic urea was also explored (Table 3). Notably, aromatic ureas bearing either electron donating or electron withdrawing groups at *ortho*, *meta*, or *para* positions experience C–N bond formation commonly. Use of Cs_2CO_3 as the base in optimized condition observed with the existence of a base susceptible functional group to be well tolerated. The beneficial of Cs_2CO_3 that it is pleasant with functional group during reaction.[11] Aromatic ureas containing electron withdrawing groups coupled well with rational yields. While Aromatic ureas bearing electron

Table 2
Results of the reaction of a variety of heteroarenol with phenyl urea[a]



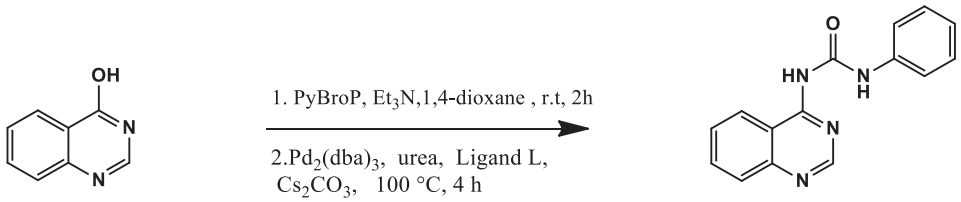
Entry	Heteroarenol	Product	Yield[b] (%)
1			97
2			95
3			91
4			89
5			90
6			93
7			85
8			90

[a] Conditions: 1. *Phosphonium coupling*: 4-quinazolinone (1 mmol), PyBroP (1.5 mmol), and Et_3N (2.0 mmol) in 1,4-dioxane (5 mL) at room temperature for 2 h; then 2. *Pd catalyzed C–N coupling*: $Pd_2(dba)_3$ (3.3 mol %), phenyl urea(1 mmol), Ligand L (5 mol %) Cs_2CO_3(1.4 mmol), and water (1 mL) at 100 °C for 4 h.
[b] Isolated yield.

donating groups were successfully coupled and resulted into excellent yields. The C–N bond coupling reaction was studied for coupling of benzyl urea and result was obtained as productively. Finally, carrying out the coupling reaction was also effective with cyclic urea as well as acyclic urea given that in slightly lower yields the correspondingly bis-heteroarylated urea products. The catalyst system was also capable to couple of benzene sulfonyl urea.

We sought to demonstrate utility of reaction to showcase such a facile, efficient, and chemo-selective of C–OH bond activation in the synthesis of biologically important nucleosides based compound such as (Phenylethynyl)-1-deoxy-1-[6-[[[(4-methoxyphenyl)-amino] carbonyl]amino]-9*H*-purin-9-yl]-*N*-ethyl-D-ribofuranuronamide.[12] Which was known as A1 and A3 Adenosine receptor agonists. It generally takes multi step to be synthesized. We felt that our

Table 3
Results of the reaction of 4-quinazolinone with a variety of ureas[a]



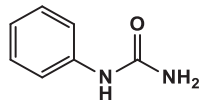
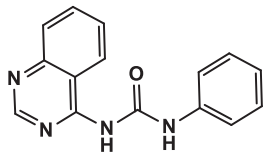
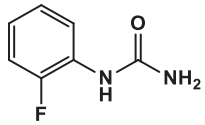
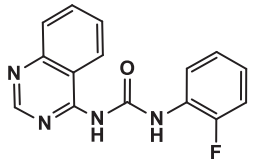
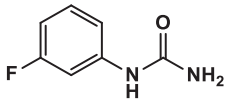
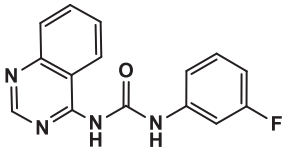
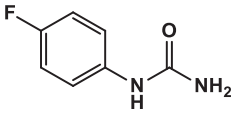
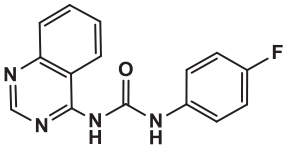
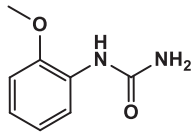
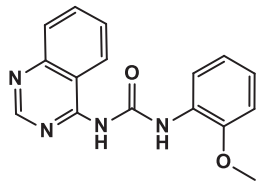
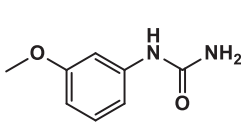
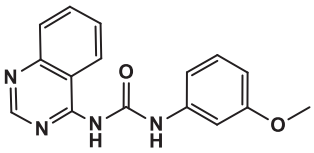
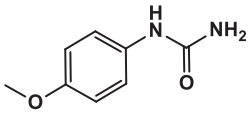
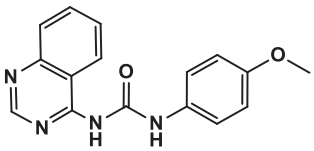
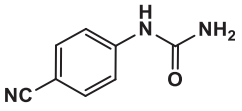
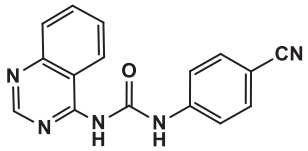
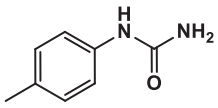
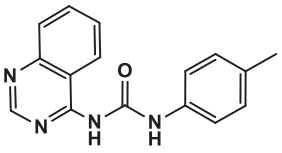
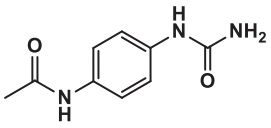
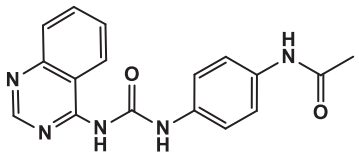
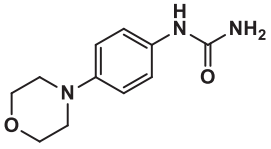
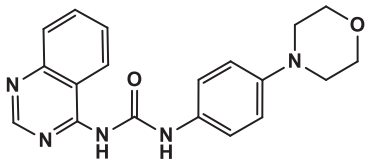
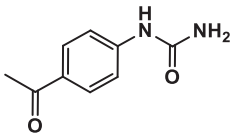
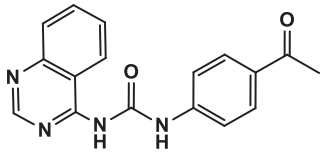
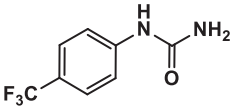
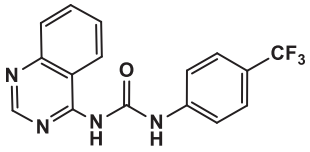
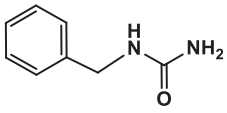
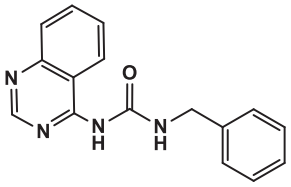
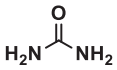
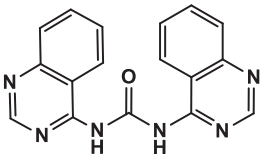
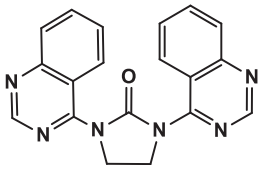
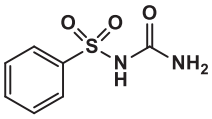
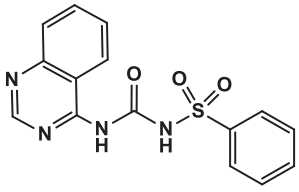
Entry	Urea	Product	Yield[b] (%)
1			97
2			83
3			85
4			79
5			95
6			89
7			96
8			77
9			81

Table 3 (*continued*)

Entry	Urea	Product	Yield[b] (%)
10			87
11			94
12			73
13			70
14			86
15[c]			77
16[c]			69
17			67

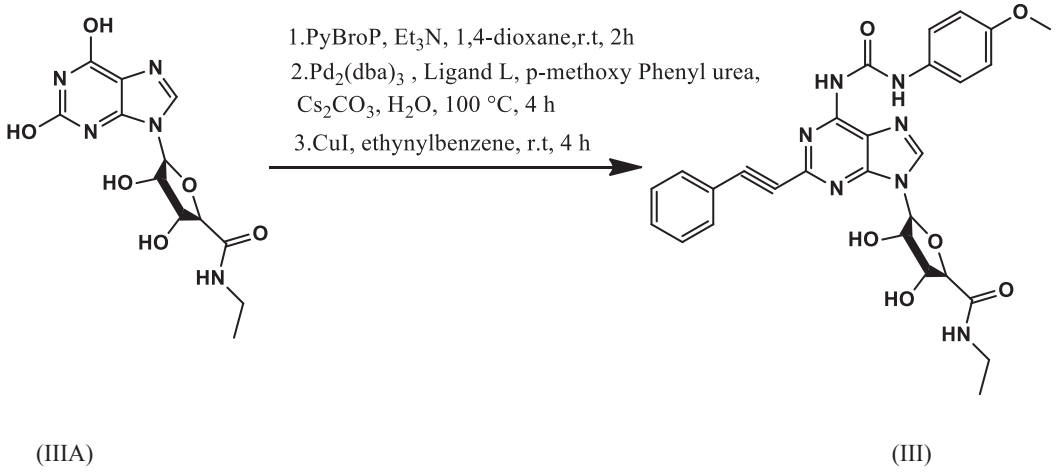
[a] Conditions: 1. *Phosphonium coupling*: 4-quinazolinone (1 mmol), PyBroP (1.5 mmol), and Et_3N (2.0 mmol) in 1,4-dioxane (5 mL) at room temperature for 2 h; then 2. *Pd catalyzed C–N coupling*: $Pd_2(dba)_3$ (3.3 mol %), urea(1 mmol), Ligand L (5 mol %) Cs_2CO_3(1.4 mmol), and water (1 mL) at 100 °C for 4 h.

[b] Isolated yield.

[c] 1. *Phosphonium coupling*: 4-quinazolinone (1 mmol), PyBroP (1.5 mmol), and Et_3N (2.0 mmol) in 1,4-dioxane (7 mL) at room temperature for 2 h; then 2. *Pd catalyzed C–N coupling*: $Pd_2(dba)_3$ (6.6 mol %), urea(1 mmol), Ligand L (10 mol %) Cs_2CO_3(2.8 mmol), and water (1.5 mL) at 100 °C for 4 h.

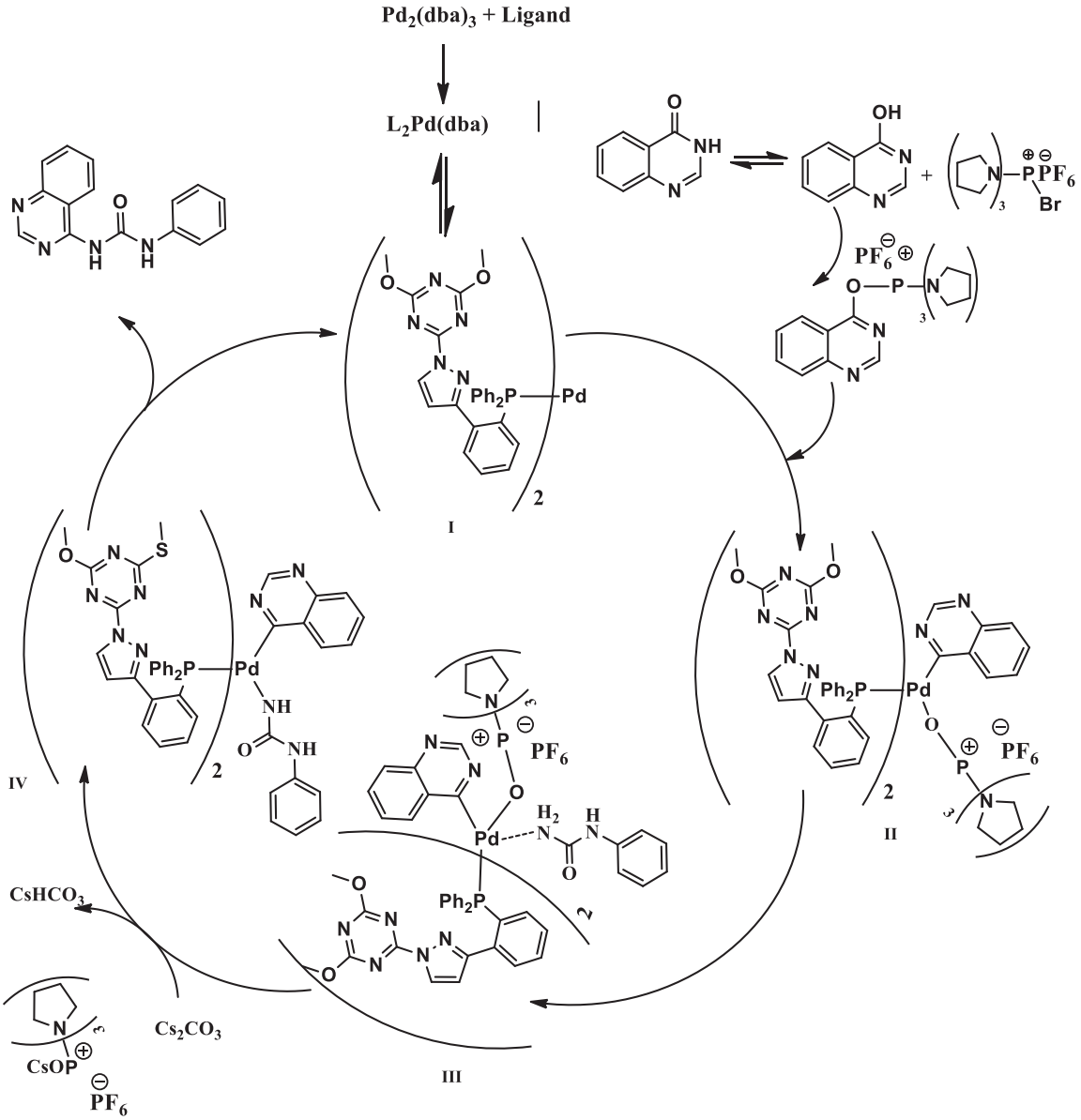
chemistry could assist the synthesis of this compound. Therefore, we chose to resynthesize compounds by using the phosphonium coupling, Pd-catalyzed C–N coupling and then sonogashira coupling at sequence in one pot synthesis (Scheme 1).

Proposed the promising mechanism of the direct dehydrative cross-coupling of 4-quinazolinone with phenyl urea via Pd catalyzed phosphonium coupling and then C–N coupling (Scheme 2). The triazine based phosphine ligand stabilized



(IIIA) (III)

Scheme 1. One pot single step synthesis of (Phenylethynyl)-1-deoxy-1-[6-[[[(4-methoxyphenyl)-amino]carbonyl]amino]-9*H*-purin-9-yl]-*N*-ethyl-D-ribofuranuronamide.



Scheme 2. Plausible mechanism.

catalytically active Pd^0 species. The tautomerization of 4-quinazolinone to 4-quinazolinol in the presence of Et_3N churn out and then PyBroP generate the heterocycle-phosphonium intermediate to activate of 4-quinazolinol (C–OH bond activation). Oxidative insertion of Pd^0 catalyst to the C–O bond of the heterocycle-phosphonium intermediate began catalytic and turned out the adduct heterocycle-Pd^{II}-phosphonium species. As a homogeneous-Pd species, this was followed by coordination of phenyl urea to heterocycle-Pd II-phosphonium species. Abstraction of the hydrogen by Cs_2CO_3 and reductive elimination produce the heteroaryl-urea product with regeneration of the Pd^0 catalyst.

3. Conclusion

In conclusion, we have developed the first Pd catalyzed C–N coupling of heteroarenols with ureas via in situ C–OH bond activation using phosphonium salt with a feasible, broad, and extremely efficient catalyst system. The flexible reaction condition and straightforward exploitation cause to be an enormously effective methodology. The scope of the reaction has been shown to tolerate both a diverse range of functionalized ureas and a variety of heteroarenols in fair to good yields. The results would be of immense attention because, of the perception used to improve the synthetic efficiency in modern organic chemistry, the combination of multi-step synthesis into a one-pot operation and/or achieving he reaction has been standard as the especially effective way for atom-efficient and environmentally benign synthesis. Consequently, these methods should find practical applications in pharmaceuticals, functional materials, catalysts, and coordination and supramolecular chemistry. Further investigations to inflate the scope of related reaction are currently in progress. Henceforth, our future endeavored will also be determined the consistent mechanism for this type of transformation.

4. Experimental section

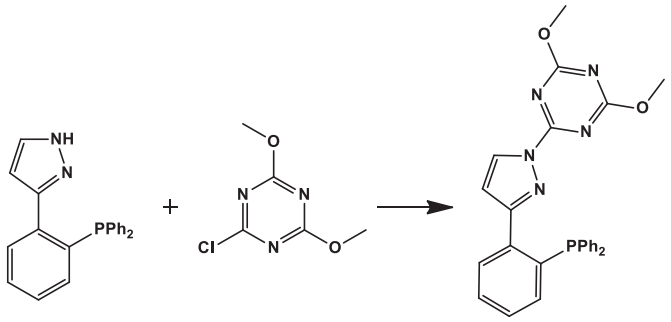
4.1. Reagents

All reactions were carried out under a nitrogen atmosphere. Air- and moisture-sensitive solvents and solutions were transferred via syringe or stainless steel cannula. All chemicals were purchased from sigma Aldrich, merck, and fluka. Solvents used were of analytical grade. Anhydrous potassium carbonate was stored in a nitrogen-filled glove-box, ground and was taken out in small quantities and stored in a desiccator. Aryl ureas were prepared by known methods.[13] All reactions were routinely checked by TLC. TLC was performed on aluminum-backed silica gel plates (silica gel 60 F_{254} grade, Merck DC) with spots visualized by UV light. Column chromatography was performed on silica gel LC 60A (70–200 micron).

4.2. Instrumental

All compounds were characterized by ^1H NMR, ^{13}C NMR as well as elemental analysis. Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker400 MHz model spectrometer usingDMSO-d6 as a solvent and TMS as internal standard with 1H resonant frequency of 400 MHz and ^{13}C resonant frequency of 100 MHz. The ^1H NMR, ^{13}C NMR chemical shifts were reported as parts per million (ppm) downfield from TMS (Me4Si). The splitting patterns are designated as follows; s, singlet; d, doublet; t, triplet; m, multiplet. Elemental analyses (C, H, N) were performed using a Heraeus Carlo Erba 1180 CHN analyzer (Hanau, Germany).

4.3. Preparation of ligand L(2-(3-(2-(diphenylphosphino) phenyl)-1*H*-pyrazol-1-yl)-4,6-dimethoxy-1,3,5-triazine)



(IA) (IB) (L)

Compound (IA) and (IB) were synthesized according to the literature method without modification.[14,15] IA (1.0 mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine(1.0 mmol), and $NaHCO_3$(1.0 mmol) were placed in a 25-mL round-bottomed Schlenk flask. After the air in the flask was replaced by nitrogen, dried and degassed Ethanol (10 mL) was added. The mixture was stirred overnight under nitrogen atmosphere at reflux temperature. After being cooled to room temperature, the solution was diluted by 10 mL of ethanol. The solvent was evaporated under vacuum. The residue was purified with silica gel column chromatography and recrystallized from n-hexane to afford ligand **L**.

^1H NMR (400 MHz, DMSO-d_6) δ ppm: 7.85–7.29 (m, 14H), 7.10 (t, J=7.2 Hz, 1H), 6.64 (d, J=1.5 Hz, 1H), 3.85 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 172.45, 169.01, 152.33, 139.10, 138.00, 133.97, 132.87, 132.66, 132.34, 130.77, 130.0, 129.89, 129.57, 126.90, 103.0, 55.0.

4.4. General procedure of reaction conditions screening

To an oven dried flat-bottomed flask, which was equipped with a magnetic stir bar, was charged with 4-quinazolinone (1 mmol), phosphonium salt (1.50 mmol), triethyl amine (2.0 mmol)in dried solvent (5.0 mL).The reaction was sparged with nitrogen for 15 min, stirred and heated to rt for 2 h. The reaction was then recharged with phenyl urea (1.00 mol), base (1.4 mmol), ligand (5 mol%), catalyst (3.3 mol%). The mixture was stirred at 100 °C for 4 h. After completion of the reaction, mixture was cooled to room temperature and filtered through a pad of Celite eluting with ethyl acetate. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

4.5. General procedures coupling reactions

To an oven dried flat-bottomed flask, which was equipped with a magnetic stir bar, was charged with heteroarenol (1 mmol), PyBroP (1.50 mmol), triethyl amine (2.0 mmol)in dried 1,4-dioxane (5.0 mL).The reaction was sparged with nitrogen for 15 min, stirred and heated to rt for 2 h. The reaction was then recharged with urea (1.00 mol), Cs_2CO_3 (1.4 mmol), ligand L (5 mol%), $Pd_2(dba)_3$(3.3 mol%), water (1 mL). The mixture was stirred at 100 °C for 4 h. After completion of the reaction, mixture was cooled to room temperature and filtered through a pad of Celite eluting with ethyl acetate. The filtrate was concentrated and

purification of the residue by silica gel column chromatography gave the desired product.

4.6. Synthesis of (phenylethynyl)-1-deoxy-1-[6-[[[(4-methoxyphenyl)-amino]carbonyl] amino]-9*H*-purin-9-yl]-*N*-ethyl-D-ribofuranuronamide

Compound (IIA) was synthesized using xanthosine according to the literature method without modification.[16] To an oven dried flat-bottomed flask, which was equipped with a magnetic stir bar, was charged with(IIIA) (1 mmol), PyBroP (3.00 mmol), triethyl amine (4.0 mmol)in dried 1,4-dioxane (10 mL).The reaction was sparged with nitrogen for 15 min, stirred and heated to rt for 2 h. The reaction was then recharged with *p*-methoxy phenyl urea (1.00 mol), Cs_2CO_3 (3.0 mmol), ligand L (6 mol %), $Pd_2(dba)_3$(3.5 mol %), water (2 mL). The mixture was stirred at 100 °C for 4 h. After completion of the reaction, mixture was cooled to room temperature and then added to CuI (2.5 mol %), ethynylbenzene (1 mmol), stirred and heated to rt for 4 h. After completion of the coupling reaction, mixture was filtered through a pad of Celite eluting with ethyl acetate. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product in 77% yield.

4.7. Characterization of coupling yield

4.7.1. 1-Phenyl-3-(quinazolin-4-yl) urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.45 (s, 1H), 9.12 (s, 1H), 8.27 (s, 1H), 7.64 (m, 2H), 7.40 (m, 4H), 7.21 (t, *J*=7.5 Hz, 2H), 6.96 (tt, *J*=7.4, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.00, 156.50, 154.00, 152.12, 141.15, 131.10, 129.07, 127.30, 126.34, 125.00, 121.41, 118.20, 113.15. Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.20; H, 4.52; N, 21.18. mp 238–239 °C.

4.7.2. 1-Phenyl-3-(quinoxalin-2-yl) urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.49 (s, 1H), 9.20 (s, 1H), 8.38 (s, 1H), 7.83 (m, 2H), 7.60 (m, 2H), 7.46 (d, *J*=7.6 Hz, 2H), 7.21 (t, *J*=7.5 Hz, 2H), 6.91 (tt, *J*=7.4, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 156.55, 156.00, 141.08, 137.99, 137.12, 134.15, 131.10, 129.02, 127.30, 126.34, 125.00, 121.45, 118.19. Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.20; H, 4.55; N, 21.16. mp 220–221 °C.

4.7.3. 1-Phenyl-3-(thieno[2,3-d]pyrimidin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.50 (s, 1H), 9.17 (s, 1H), 8.28 (s, 1H), 7.78 (d, *J*=6.2 Hz, 1H), 7.67 (d, *J*=6.2 Hz, 1H), 7.46 (d, *J*=7.6 Hz, 2H), 7.30 (t, *J*=7.6 Hz, 2H), 7.01 (t, *J*=7.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.00, 156.00, 154.00, 152.12, 141.14, 129.05, 124.45, 122.15, 121.44, 121.00, 118.13. Anal. Calcd for $C_{13}H_{10}N_4OS$: C, 57.76; H, 3.73; N, 20.73. Found: C, 57.70; H, 3.75; N, 20.70. mp 217 °C.

4.7.4. 1-Phenyl-3-(pyridazin-3-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.42 (s, 1H), 8.40 (s, 1H), 8.03 (d, *J*=9.0 Hz, 1H), 7.89 (d, *J*=9.0 Hz, 1H), 7.61 (m, 1H), 7.51 (d, *J*=7.6 Hz, 2H), 7.22 (t, *J*=7.6 Hz, 2H), 7.10 (t, *J*=7.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 157.12, 156.49, 146.10, 141.03, 129.60, 129.00, 121.47, 118.17. 117.00. Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.63; H, 4.74; N, 26.19. mp 257 °C.

4.7.5. 1-(4-Methylpyrimidin-2-yl)-3-phenylurea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.47 (s, 1H), 8.33 (s, 1H), 8.22 (d, *J*=9.0 Hz, 1H), 7.21 (t, *J*=7.5 Hz, 2H), 7.43 (d, *J*=7.5 Hz, 2H), 7.0 (m, 2H) 2.72 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 169.00, 157.82, 156.58, 155.10, 141.08, 129.04, 121.41, 118.19, 116.34, 25.15. Anal. Calcd for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.14; H, 5.27; N, 24.57. mp 262 °C.

4.7.6. 1-Phenyl-3-(pyrimidin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.50 (s, 1H), 8.79 (s, 1H), 8.41 (s, 1H), 8.08 (d, *J*=9.0 Hz, 1H), 7.42 (d, *J*=7.6 Hz, 2H), 7.23 (t, *J*=7.5 Hz, 2H), 6.99 (t, *J*=7.5 Hz, 1H), 6.40 (d, *J*=9.0, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 158.62, 158.00, 156.60, 155.90, 141.00, 129.00, 121.42, 118.22, 109.10. Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.64; H, 4.75; N, 26.17. mp 243 °C.

4.7.7. 1-(5-Methyl-4H-pyrazol-3-yl)-3-phenylurea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.48 (s, 1H), 8.30 (s, 1H), 7.59 (d, *J*=7.6 Hz, 2H), 7.43 (t, *J*=7.6 Hz, 2H), 6.69 (t, *J*=7.4 Hz, 1H), 3.43 (s, 2H), 3.01 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm; 158.12, 156.48, 151.80, 141.05, 131.10, 129.05, 121.48, 33.05, 22.15. Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.06; H, 5.60; N, 25.95. mp 211 °C.

4.7.8. 1-(Benzo[d]thiazol-2-yl)-3-phenylurea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.49 (s, 1H), 8.35 (s, 1H), 7.97 (d, *J*=9.0 Hz, 1H), 8.00 (d, *J*=9.0 Hz, 1H), 7.51 (m, 4H), 7.24 (d, *J*=7.5 Hz, 2H), 6.94 (t, *J*=7.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 156.40, 154.49, 151.02, 141.03, 133.11, 129.04, 125.10, 123.34, 121.48, 120.30, 118.11, 117.15. Anal. Calcd for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.44; H, 4.17; N, 15.57. mp 232 °C.

4.7.9. 1-(2-Fluorophenyl)-3-(quinazolin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.50 (s, 1H), 9.11 (s, 1H), 8.41 (s, 1H), 7.69 (dd, *J*=7.6, 5.7 Hz, 1H), 7.21 (m, 5H), 7.01 (td,*J*=7.6, 5.8 Hz, 1H), 6.80 (tdd, *J*=7.7, 5.7, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.03, 155.53–155.35 (m), 154.05, 152.99, 152.10, 131.09 (d, *J*=8.4 Hz), 130.08, 128.99 (d, *J*=19.8 Hz), 127.32, 126.30, 125.98 (d, *J*=2.9 Hz), 125.01, 122.74 (d, *J*=7.6 Hz), 121.88 (d, *J*=19.8 Hz), 113.12. Anal. Calcd for $C_{15}H_{11}FN_4O$: C, 63.83; H, 3.93; N, 19.85. Found: C, 63.86; H, 3.90; N, 19.83. mp 244 °C.

4.7.10. 1-(3-Fluorophenyl)-3-(quinazolin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.52 (s, 1H), 9.13 (s, 1H), 9.46 (s, 1H), 7.83 (dt, *J*=9.0, 2.0 Hz, 1H), 7.58 (m, 2H), 7.42 (m, 1H), 7.35 (td, *J*=7.6, 5.8 Hz, 1H), 7.19 (m, 1H), 6.83 (ddt, *J*=11.0, 7.8, 2.1 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.0, 164.02,161.52, 156.37, 154.00, 152.11, 140.91 (d, *J*=7.6 Hz), 131.17, 130.03(d, *J*=7.6 Hz), 127.33, 126.33, 125.08, 116.60 (d, *J*=2.9 Hz), 113.18, 111.46 (d, *J*=19.8 Hz), 106.64 (d, *J*=19.8 Hz). Anal. Calcd for $C_{15}H_{11}FN_4O$: C, 63.83; H, 3.93; N, 19.85. Found: C, 63.82; H, 3.97; N, 19.81. mp 242 °C.

4.7.11. 1-(4-Fluorophenyl)-3-(quinazolin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.50 (s, 1H), 9.13 (s, 1H), 8.57 (s, 1H), 7.66 (dd,*J*=7.6, 2.0 Hz, 1H), 7.53 (td, *J*=7.5, 2.0 Hz, 1H), 7.36–7.28 (m, 4H), 6.97–7.06 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.04, 161.49, 159.00, 156.65, 154.04, 152.19, 139.71 (d, *J*=2.9 Hz), 131.13, 127.29, 126.38, 125.07,119.63 (d, *J*=8.4 Hz), 114.57 &114.37 (d, *J*=21 Hz), 113.20. Anal. Calcd for $C_{15}H_{11}FN_4O$: C, 63.83; H, 3.93; N, 19.85. Found: C, 63.80; H, 3.96; N, 19.90. mp 247–248 °C.

4.7.12. 1-(2-Methoxyphenyl)-3-(quinazolin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.38 (s, 1H), 9.15 (s, 1H), 9.04 (s, 1H), 7.75 (td, *J*=7.6, 2.0 Hz, 1H), 7.48 (m, 2H), 7.40 (m, 1H), 7.20 (dd, *J*=7.2, 2.1 Hz, 1H), 7.17–7.12 (m, 2H) 7.00 (dd, *J*=7.8, 1.9 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.98, 156.62, 154.05, 153.05, 152.09, 131.08, 129.40, 127.38, 126.37, 125.30, 125.05, 124.13, 120.69, 113.74, 113.17, 56.60. Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.33; H, 4.84; N, 19.00. mp 234 °C.

4.7.13. 1-(3-Methoxyphenyl)-3-(quinazolin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:9.41 (s, 1H), 9.14 (s, 1H), 8.37 (s, 1H), 7.77

(dd, J=7.6, 2.0 Hz, 1H) 7.50 (m, 2H), 7.34 (m, 2H), 7.22 (t, J=8.0 Hz, 1H), 6.98 (dd, J=8.0, 2.0 Hz, 1H), 6.60 (dd, J=8.0, 2.0 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm:166.05,159.15, 156.57, 153.99, 152.07, 141.27, 131.16, 129.67, 127.26, 126.39, 125.07, 116.36, 113.18, 113.09, 107.47, 56.57. Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.84; H, 4.58; N, 9.01. mp 230–231 °C.

4.7.14. 1-(4-Methoxyphenyl)-3-(quinazolin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.40 (s, 1H), 9.10 (s, 1H), 8.90 (s, 1H), 7.70 (dd, J=7.6, 2.0 Hz, 1H) 7.52 (m, 2H), 7.41 (d, J=7.6 Hz, 2H), 7.30 (m, 1H), 6.83 (d, J=7.6 Hz, 2H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.06, 159.98, 156.70, 154.08, 152.17, 137.57, 131.18, 127.36, 126.38, 125.00, 119.58, 114.38, 113.19, 56.57. Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.35; H, 4.77; N, 19.02. mp 237 °C.

4.7.15. 1-(4-Cyanophenyl)-3-(quinazolin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.52 (s, 1H), 9.09 (s, 1H), 8.90 (s, 1H),8.20 (d, J=8.6 Hz, 2H), 7.79 (m, 2H), 7.69 (d, J=8.6 Hz, 2H), 7.90 (d, J=7.5 Hz, 1H), 7.44 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.09,156.77, 154.09, 152.17, 142.44, 133.34, 131.11, 127.36, 126.38, 125.07, 119.15, 119.00, 113.17, 107.70. Anal. Calcd for $C_{16}H_{11}N_5O$: C, 66.43; H, 3.83; N, 24.21. Found: C, 66.47; H, 3.89; N, 24.24. mp 218 °C.

4.7.16. 1-(Quinazolin-4-yl)-3-(p-tolyl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.44 (s, 1H), 9.14 (s, 1H), 9.00 (s, 1H), 7.84 (d, J=7.6 Hz, 1H), 7.66 (m, 2H), 7.46 (t, J=7.6 Hz, 1H), 7.21 (d, J=7.8 Hz, 2H), 7.00 (d, J=7.8, 2H), 2.37 (s, 3H), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.097, 156.65, 153.98, 152.09, 139.89, 137.57, 131.06, 128.77, 127.26, 126.29, 125.07, 118.92, 113.21, 22.00. Anal. Calcd for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 69.10; H, 5.05; N, 20.17. mp 225 °C.

4.7.17. N-(4-(3-(Quinazolin-4-yl)ureido)phenyl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.76 (s, 1H), 9.19 (s, 1H), 9.42 (s, 1H), 8.15 (s, 1H), 7.89 (d, J=7.5 Hz, 1H), 7.73 (d, J=7.8 Hz, 2H), 7.64 (m, 2H), 7.58 (d, J=7.8 Hz, 2H),7.41 (m, 1H). 2.11 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 170.05, 166.04, 156.53, 153.95, 152.10, 139.02, 137.89, 131.11, 127.35, 126.35, 124.95, 119.10, 119.00, 113.17, 23.53. Anal. Calcd for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79. Found: C, 63.59; H, 4.67; N, 21.74. mp 219 °C.

4.7.18. 1-(4-Morpholinophenyl)-3-(quinazolin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.43 (s, 1H), 9.20 (s, 1H), 8.76 (s, 1H), 7.65 (m, 2H), 7.50 (d, J=7.6 Hz, 2H), 7.41 (m, 1H), 7.28 (m, 1H), 6.87 (d, J=7.6 Hz, 2H), 3.70 (t, J=4.8 Hz, 4H), 3.28 (t, J=4.8 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.00, 156.47, 154.00, 152.12, 151.76, 136.06, 131.10, 127.30, 126.34, 125.00, 120.56, 118.40, 113.15, 67.00, 49.80. Anal. Calcd for $C_{19}H_{19}N_5O_2$: C, 65.32; H, 5.48; N, 20.04. Found: C, 65.35; H, 5.50; N, 20.07. mp 249 °C.

4.7.19. 1-(4-Acetylphenyl)-3-(quinazolin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.47 (s, 1H), 9.03 (s, 1H), 8.64 (s, 1H), 7.94 (d, 8.2 Hz, 2H), 7.85 (d, 8.2 Hz, 2H),7.75 (d, J=7.6 Hz, 1H), 7.62 (m, 2H), 7.41 (t, J=7.6 Hz, 1H),2.60 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 197.86, 166.00, 156.76,1 54.03, 152.02, 141.53, 135.53, 131.13, 128.77, 127.35, 126.37, 125.02,118.65, 113.15, 25.77. Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.63; H, 4.69; N, 18.25. mp 227 °C.

4.7.20. 1-(Quinazolin-4-yl)-3-(4-(trifluoromethyl)phenyl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.49 (s, 1H), 9.11 (s, 1H), 8.08 (s, 1H), 7.91 (d, J=8.8 Hz, 2H), 7.82 (d, J=7.5 Hz, 1H), 7.68 (m, 2H), 7.50 (d, J=8.8 Hz, 2H),7.30 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.06, 156.81, 154.00, 152.13, 143.48, 132.54, 132.23, 131.17, 127.36, 126.31, 126.77 (m), 125.00, 124.01, 119.70 (d, J=2.2 Hz), 113.21. Anal. Calcd for $C_{16}H_{11}F_3N_4O$: C, 57.83; H, 3.34; N, 17.15. Found: C, 57.85; H, 3.37; N, 17.20. mp 257 °C.

4.7.21. 1-Benzyl-3-(quinazolin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.69 (s, 1H), 9.06 (s, 1H), 7.96 (s, 1H), 7.88 (d, J=7.6 Hz, 1H), 7.71 (m, 2H), 7.51 (t, J=7.5 Hz, 1H), 7.25–7.11 (m, 5H), 4.33 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.94, 155.51, 154.05, 152.02, 141.14, 131.10, 128.32, 128.19, 127.38, 126.75, 126.31, 124.88, 113.19, 45.00. Anal. Calcd for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 69.08; H, 5.08; N, 20.08. mp 211–212 °C.

4.7.22. 1,3-Di(quinazolin-4-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.73 (s, 2H), 9.10 (s, 2H), 7.75 (d, J=7.8 Hz, 2H), 7.71 (d, J=7.8 Hz, 2H), 7.44–7.60 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.08, 156.78, 154.12, 152.08, 131.07, 127.27, 126.28, 124.06, 113.18. Anal. Calcd for $C_{17}H_{12}N_6O$: C, 64.55; H, 3.82; N, 26.57 Found: C, 64.50; H, 3.84; N, 26.54. mp 200 °C.

4.7.23. 1,3-Di(quinazolin-4-yl)imidazolidin-2-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.13 (s, 2H), 7.78 (d, J=7.8 Hz, 2H), 7.64 (d, J=7.8 Hz, 2H), 7.24–7.49 (m, 4H), 4.15 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.97, 152.07, 154.04, 131.15, 127.37, 126.31, 125.09, 113.10., 156.86, 56.20, 42.66. Anal. Calcd for $C_{19}H_{14}N_6O$: C, 66.66; H, 4.12; N, 24.55. Found: C, 66.64; H, 4.16; N, 24.60. mp207 °C.

4.7.24. N-(Quinazolin-4-ylcarbamoyl)benzenesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.06 (s, 1H), 8.87 (s, 1H), 7.67 (d, J=7.6 Hz, 2H), 7.47 (s, 1H), 7.25 (d, J=7.6 Hz, 2H), 7.13 (m, 3H), 6.95 (m, 1H), 6.86 (t, J=7.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.79, 155.07, 153.91, 153.00, 141.00, 133.05, 131.50, 129.12, 127.10, 126.24, 124.57, 110.19, 105.81. Anal. Calcd for$C_{15}H_{12}N_4O_3S$: C, 54.87; H, 3.68; N, 17.06. Found: C, 54.82; H, 3.71; N, 17.03. mp 208 °C.

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Supplementary data

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