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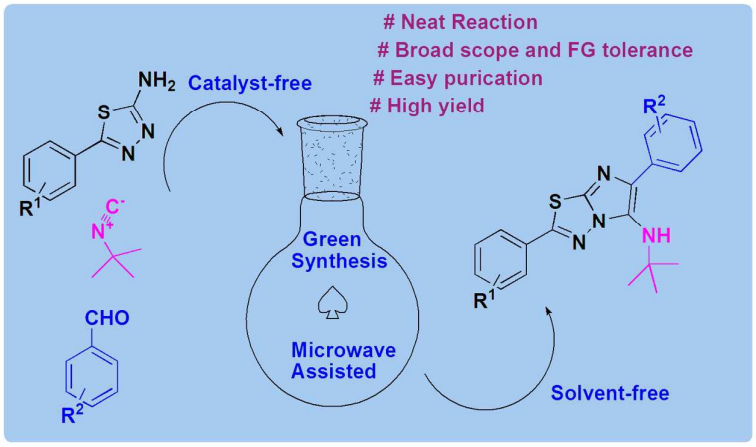
Preeti Wadhwa, Tanpreet Kaur and Anuj Sharma*

Abstract

A concise and efficient one pot synthesis of bicyclic imidazo[2,1-*b*][1,3,4]thiadiazoles *via* the three component Groebke-Blackburn-Bienaymé (GBB) reaction utilizing 5-aryl-1,3,4-thiadiazol-2-amines, aromatic aldehydes and isonitriles has been developed. The reactions were carried out under microwave irradiation and ultimate green conditions excluding both catalyst and solvent. Furthermore, the "greenness" of the protocol was evaluated within the ambits of green metrics and the method exhibited excellent score in the defined parameters such as atom economy, E-factor, reaction mass efficiency, process mass intensity and carbon efficiency. This environmentally benign GBB methodology paves an easy access towards the synthesis of pharmacologically significant scaffolds.

Graphical Abstract



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A concise and efficient one pot synthesis of bicyclic imidazo[2,1-*b*][1,3,4]thiadiazoles *via* the three component Groebke-Blackburn-Bienaymé (GBB) reaction utilizing 5-aryl-1,3,4-thiadiazol-2-amines, aromatic aldehydes and isonitriles has been developed. The reactions were carried out under microwave irradiation and ultimate green conditions excluding both catalyst and solvent. Furthermore, the "greenness" of the protocol was evaluated within the ambits of green metrics and the method exhibited excellent score in the defined parameters such as atom economy, E-factor, reaction mass efficiency, process mass intensity and carbon efficiency. This environmentally benign GBB methodology paves an easy access towards the synthesis of pharmacologically significant scaffolds.

Introduction

Fused heterocyclic structures over the last few decades have presented enormous opportunities in the field of drug design and therapeutics.[1,2] The bicyclic core of imidazo[2,1-*b*][1,3,4]thiadiazoles[3] is one such scaffold widely manifested in an array of pharmacophoric activities[4] such as antihyperlipidemic,[5] antitubercular,[6] antitumor[7] and antimicrobial activities.[8] Some representative members of this class are displayed in Fig. 1 *e.g.*, 5,6-diarylsubstituted thiazolotriazole (**I**) acts as a COX-2 inhibitor,[9] compound 2-trifluoromethyl-5,6-(4',4''-dimethoxyphenyl)imidazo [2,1-*b*][1,3,4]thiadiazole (**II**) as an antitubercular, 5-formyl-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazole sulphonamide derivatives (**III**) and 2-benzyl-6-(4'-fluorophenyl)-5-thiocyanato-imidazo[2,1-*b*][1,3,4]thiadiazole (**IV**) as potent anti-cancer agents.

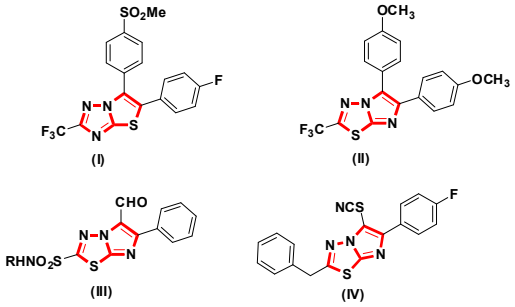

Fig. 1 Structures of pharmaceutically important imidazo[2,1-*b*][1,3,4]thiadiazoles.

From a synthetic point of view, to date, the routes for the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazoles are rather limited. In literature, this core was mainly synthesized by employing classical methods involving substituted 1,3,4-thiadiazol-2-amines and their reaction with a variety of reagents *e.g.* functionalized α-haloketones,[10,11] α-haloacetic acid,[12] chloroacetyl chloride,[13] acetophenones[14] and *N*, *N*-dimethylformamide dimethyl acetal.[15] These classical methodologies possess several disadvantages, including the use of organic solvents, detrimental reagents, long reaction time, cumbersome work up procedures and moderate yields. Moreover, these methodologies are not well suited for a diversity oriented synthesis of imidazo[2,1-*b*][1,3,4]thiadiazole scaffolds.

In the past decade, **M**icrowave-**A**ssisted **O**rganic **S**ynthesis (MAOS) has gained prominence, particularly in developing sustainable catalyst-free and solvent-free versions of tedious reactions (CFR & SFR). Moreover and quite frequently, these approaches result in pollutant reduction, drastic reduction in reaction times, and formations of relatively pure products thereby avoiding tedious column chromatography. Hence it represents a powerful green alternative to conventional synthesis.[16]

In this context, microwave-assisted multi-component Groebke-Blackburn-Bienaymé (GBB)[17] can be a promising approach towards synthesis of imidazo[2,1-*b*][1,3,4]thiadiazoles. With this, we had hoped to harvest some of the benefits associated with MAOS as stated above.

Surprisingly, there are only couple of reports for syntheses of imidazo[2,1-*b*][1,3,4]thiadiazoles through GBB route. First in the seminal report by Bienaymé *et al.*,[18] where a single

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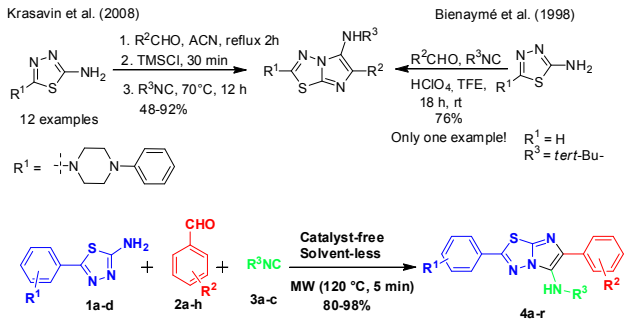
example of *N-tert*-butyl-6-phenyl-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-5-amine was generated using perchloric acid as catalyst in trifluoroethanol, and second by Krasavin *et al.,*[19] where 5-piperazin-1-yl-1,3,4-thiadiazol-2-amines were synthesized using trimethylsilyl chloride as a promoter in acetonitrile (Scheme 1). Hence there is a sufficient scope for improvement of this reaction in terms of scope, reactions conditions and environment friendliness.

In continuation with our constant quest aimed at utilizing known isocyanide-based MCRs for creating libraries in a combinatorial fashion,[20] we herein propose a straightforward, catalyst-free and solvent-less method that can easily access diversity-oriented imidazo[2,1-*b*][1,3,4]thiadiazoles *via* successive cyclisation of 5-aryl-1,3,4-thiadiazol-2-amines, aromatic aldehydes, and isonitriles under microwave irradiation (Scheme 1).



R^1, R^2 = H, electron-donating, electron-withdrawing groups.

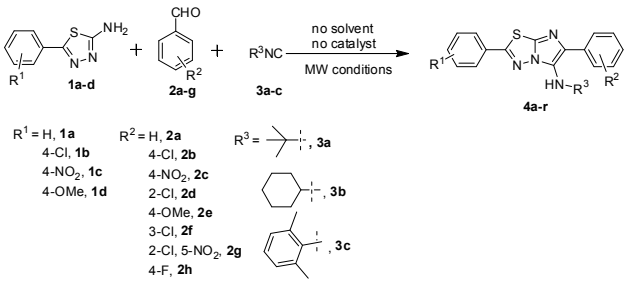
R^3 = aliphatic, alicyclic, aromatic groups.

Scheme 1 One pot three-component synthesis of 2-arylimidazo[2,1-*b*][1,3,4] thiadiazoles.

Moreover, most of the products were crystallized out from the crude reaction mixture in high yields and purity.

Results and Discussion

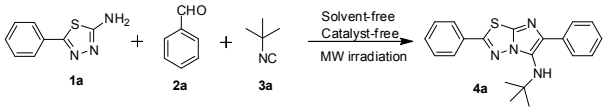
In a pursuit to develop a catalyst and solvent-free approach for the synthesis of 2-arylimidazo[2,1-*b*][1,3,4]thiadiazoles (Scheme 2).



Scheme 2 A Microwave Assisted protocol for the synthesis of 2-arylimidazo[2,1-*b*][1,3,4]thiadiazoles.

We started our investigation with the optimization of three-component GBB reaction using 5-phenyl-1,3,4-thiadiazol-2-amines **1a** (0.25 mmol), benzaldehyde **2a** (0.27 mmol) and *N-tert*-butyl isonitrile **3a** (0.30 mmol) as model substrates (Table 1) under microwave irradiation. Initially, the reaction was carried out at a mild temperature of 40 °C for 30 minutes in a sealed vial excluding solvent and catalyst (Table 1, entry 1). The reaction did not proceed at all and the starting materials remained completely unconsumed. However, by increasing the temperature to 80 °C, the desired product **4a** was formed in moderate yields (61%) with still some unreacted starting material.

Table 1 Optimization of the reaction conditions for the synthesis of *N-tert*-butyl-2,6-diphenylimidazo [2,1-*b*][1,3,4]thiadiazol-5-amine **4a**[a]



Entry	Temperature (°C)[b]	Time (min)	Yield (%)[c]
1	40	10	nr*
2	80	10	61
3	100	10	73
4	120	10	98
5	140	10	85
6	160	10	87
7	**120**	**5**	**98**
8	120	2	90

[a]General condition: 5-phenyl-1,3,4-thiadiazol-2-amines **1a** (0.25 mmol); benzaldehyde **2a** (0.27 mmol); *N-tert*-butyl isonitrile **3a** (0.3 mmol); [b]Anton Paar Monowave 300 reactor. Irradiation Power: 850 W; Ramp time: 1 min. 60 °C; [c]Isolated yield by recrystallization, *no reaction.

Next, the reaction was conducted at various temperatures *viz.* 120 °C, 140 °C and 160 °C for 10 min, furnishing the products in 98%, 85% and 87% yields, respectively (Table 1, entries 4-6). Furthermore, to reduce the reaction time, the reaction mixture was irradiated at 5 and 2 minutes interval which furnished the product in 98% and 90% yield, respectively (Table 1, entries 7-8). Following this examination, the best result was obtained at 120 °C, which yielded the product **4a** in 98% yield under 5 minutes of microwave irradiation (Table 1, entry 7). It is particularly advantageous; since the reaction is selective and quantitative, the product form exclusively and no column purification is required in most of the cases. The optimization of reaction yields *versus* the reaction temperature is mentioned in Fig. 2.

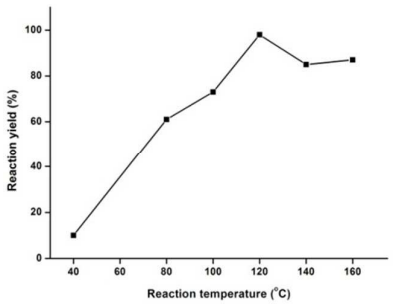


Fig. 2 Reaction temperature *vs.* Reaction yield (%) for the synthesis of *N-tert*-butyl-2,6-diphenylimidazo[2,1- *b*][1,3,4]thiadiazol-5-amine **4a**.

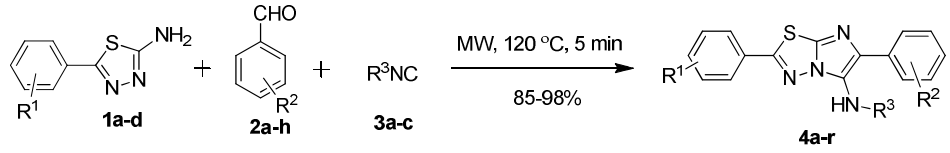
After corroborating the feasibility of the reaction, the scope and robustness of this one-pot three-component domino 2-arylimidazo[2,1-*b*][1,3,4]thiadiazoles synthesis was evaluated by employing a diverse range of 5-aryl-1,3,4-thiadiazol-2-amines, aldehydes and isocyanides (Table 2). To see the effect of heteroatom on the amine functionality towards the reaction efficiency, we attempted the reaction with 5-aryl-1,3,4-oxadiazol-2-amine and observed that it failed to provide the respective product **4s** (0%) and only starting material was recovered.

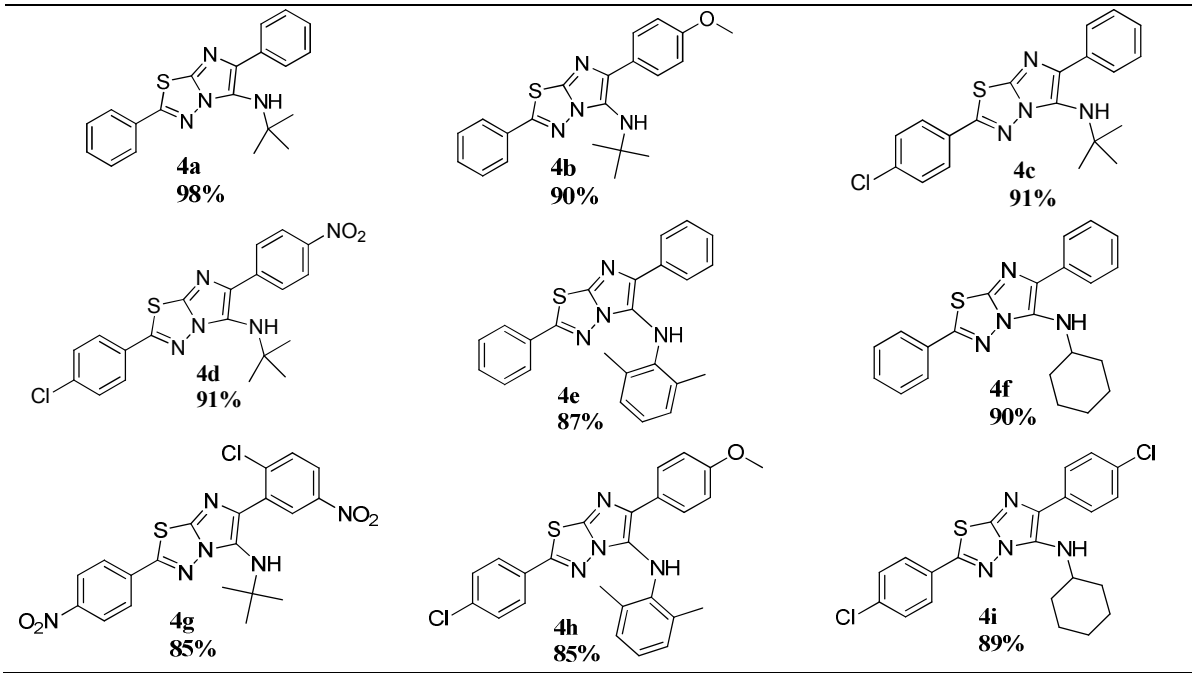
The electronic nature of the 5-substituted-1,3,4-thiadiazol-2-amines and aldehydes had an impact on the reaction efficiency. It was found that a variety of 5-aryl-1,3,4-thiadiazol-2-amines derived from benzoic acid containing both electron-donating and electron-withdrawing groups on the phenyl ring were employed and were well tolerated under the optimal reaction conditions. 5-aryl-1,3,4-thiadiazol-2-amines having electron-donating groups *e.g.*, methoxy **4o** (85%) & **4p** (87%) and chloro **4c** (91%) & **4d** (91%), *etc.* resulted in good yields of the product. On the contrary, electron-withdrawing groups on the amine functionality *e.g.*, nitro **4g** (85%) & **4l** (85%) yielded slightly lower yields.

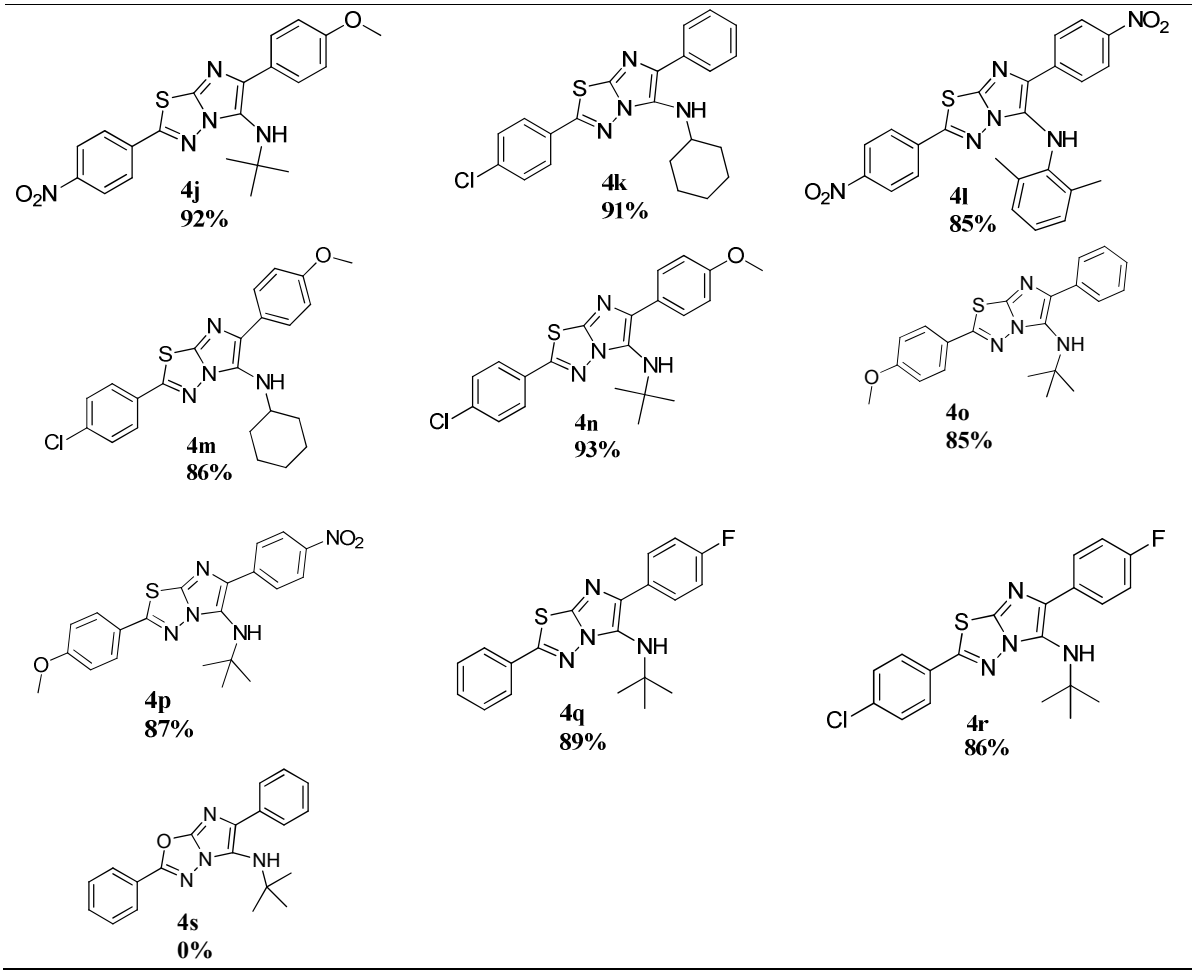
Diverse aromatic aldehydes (electron-donating as well as electron-withdrawing) were also well accommodated. It is worth mentioning that aromatic aldehydes with an electron-withdrawing group *viz.* nitro **4d** (91%), **4p** (87%) and fluoro **4q** (89%) & **4r** (86%) *etc.* resulted in good yields of the product as expected. However, aromatic aldehydes bearing electron-donating substituents *e.g.* methoxy **4b** (90%), **4h** (85%) *etc.* also well accepted. Therefore, the present methodology works well with both activated and deactivated systems. It is worth mentioning that deactivating systems containing *e.g.* nitro & fluoro also gave excellent yields without adding any catalyst or promoters as utilized in Krasavin *et al.* method[19] and in this context, it scores over it.

Similarly, the reaction seemed well tolerant to a range of isocyanides *e.g.* aliphatic (*N*-*tert*-butyl), alicyclic (cyclohexyl) and aromatic (2,6-dimethylphenyl) isocyanides. From the results, it seemed that the reaction worked efficiently and smoothly with *N*-*tert*-butyl and 2,6-dimethylphenyl isocyanides resulting in crystallization of the pure products. However, reactions employing cyclohexyl isocyanide **4f** (90%), **4i** (89%), **4k** (91%) & **4m** (86%) required column chromatography to isolate the pure products, albeit in excellent yields.

Table 2 Library of 2-arylimidazo[2,1-*b*][1,3,4]thiadiazoles *via* the one-pot GBB condensation.

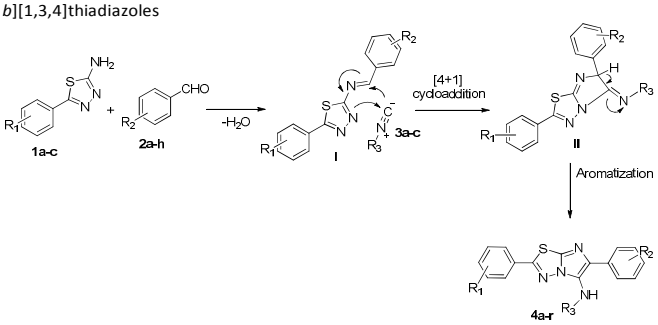






The structure of all the newly synthesized imidazo[2,1-*b*][1,3,4]thiadiazoles were deduced by their satisfactory spectral data (^{1}H, ^{13}C NMR and HRMS). By taking the entire experimental outcome into consideration, a plausible mechanistic pathway for the synthesis of 2-arylimidazo[2,1-*b*][1,3,4]thiadiazoles is outlined in Scheme 3. The first step is believed to be the imine (**I**) formation by the reaction of 5-aryl-1,3,4-thiadiazol-2-amines **1a-d** and aldehyde **2a-h**, followed by trapping of the imine carbon by isocyanides **3a-c** through [4 +1] cycloaddition, yields nitrilium ion intermediate (**II**), which upon aromatization forms 2-arylimidazo[2,1-*b*][1,3,4] thiadiazoles (**4a-r**).

Scheme 3 Tentative reaction mechanism for the synthesis of 2-arylimidazo[2,1-*b*][1,3,4]thiadiazoles



From the standpoint of green chemistry, it would be imperative to evaluate our chemical process as environmentally benign, for which quantification of sustainable practices such as measuring the "greenness" of our method would be essential.[21-24] Several green metrics such as Atom Economy (AE), E-factor, Process Mass Intensity (PMI), Reaction Mass Efficiency (RME) and Carbon Efficiency (CE) has been developed which enables us to evaluate chemical processes in terms of waste, energy usage and carbon efficiency. Table 3

provides the calculation of the illustrative metrics for all the synthesized compounds.

Table 3 Summary of green metrics for the synthesized 2-arylimidazo[2,1-*b*][1,3,4]thiadiazoles[a]

S. No.	Yield (%)	%AE	%CE	E-factor[a]	% RME	PMI
4a	98	95.08	89.65	0.153	86.05	1.153
4b	90	95.45	82.85	0.252	79.74	1.252
4c	91	95.50	83.83	0.228	81.39	1.228
4d	91	95.96	82.91	0.240	80.73	1.240
4e	87	95.65	78.61	0.308	76.43	1.308
4f	90	90.35	82.15	0.261	79.32	1.261
4g	85	96.33	78.34	0.308	76.40	1.308
4h	85	96.24	76.99	0.324	75.51	1.324
4i	89	96.09	83.98	0.219	82.02	1.219
4j	92	95.92	84.70	0.209	82.66	1.209
4k	91	95.78	83.07	0.235	81.01	1.235
4l	85	96.43	76.80	0.316	75.76	1.316
4m	86	96.05	78.49	0.305	76.05	1.305
4n	93	95.82	85.47	0.201	83.26	1.201
4o	85	95.45	78.63	0.317	76.31	1.317
4p	87	95.92	80.48	0.284	77.85	1.284
4q	89	95.39	81.91	0.268	78.84	1.268
4r	86	95.72	79.26	0.299	76.98	1.299

The higher environmental compatibility factors such as smaller E-factor, higher atom economy make the present methodology an ideal green and sustainable process. Furthermore, we evaluated the greenness of our protocol with respect to existing literature reports for the synthesis of fused imidazo[2,1-*b*][1,3,4]thiadiazoles (Fig. 3), the results are collected and tabulated in Table 4. These results corroborates that our protocol for synthesis of imidazo[2,1-*b*][1,3,4]thiadiazoles has a greener profile over published traditional procedures when identical chemistries of reactions are compared. The detailed calculations are explained in the ESI.*

Table 4 A comparison of efficiency between present and reported methods for the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazoles[a]

Entry	Solvent/reaction conditions	Temp. (°C)	Time	Yield (%)	E-factor	PMI
1.	5 mol% $HClO_4$, TFE[18]	2 5	18 h	76	13.36	14.46
2.	TMSCl, ACN/DCM[19]	70	12 h	84	4.23	5.23
3.	No solvent, no catalyst	120	5 min	98	0.153	1.153

[a]Calculations upto the crude product in all cases

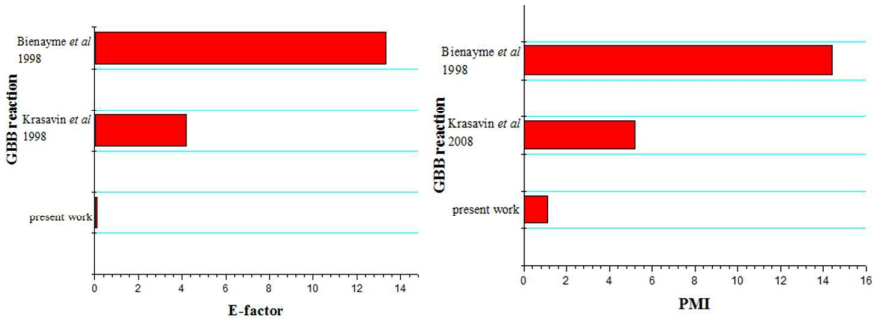


Fig. 3 E-factor and PMI profiles showing individual contributions for the synthesis of fused imidazo[2,1-*b*][1,3,4]thiadiazoles.

In summary, we report a simple and straightforward one-pot three-component catalyst and solvent free integrated protocol for the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazoles in good yields under microwave irradiation. This convergent and versatile method presents broad substrate scope and excellent functionality tolerance. This approach enables the rapid assembly of diverse imidazo[2,1-*b*][1,3,4]thiadiazoles based frameworks utilizing all the three components efficiently. More importantly, the methodology works well for both activating and deactivating starting material. This methodology therefore exemplifies the reconciliation of structural complexity and operational simplicity in an environmentally benign manner. In all the cases, but a few ones, the isolation and purification of compounds were done by mere filtration and ethanol washing which makes the process tailor made for automation in a high throughput synthetic platform. Furthermore, a variety of green metrics have been explored and our method exemplary fit in this grid.

Experimental section

General procedure for the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazole fused heterocycles (4a-r). 5-Aryl-1,3,4-thiadiazol-2-amines **1a** (0.25 mmol), aromatic aldehyde **2a** (0.27 mmol) and isocyanide **3a** (0.3 mmol) were taken in G-10 glass vial capped with Teflon septum. After a pre-stirring of 1 or 2 minutes at RT, the vial was subjected to microwave irradiation with the initial ramp time of 1 minute at 60 °C. The temperature was then raised to 120 °C with the holding time of 5 minutes. The products were recrystallized using EtOH. Some of the viscous products (**4f, 4i, 4k, 4m**) were purified by silica gel column chromatography (ethyl acetate/hexane). All compounds were fully characterized by Mp, IR, NMR, mass spectral data.

***N*–*tert*-Butyl-2,6-diphenylimidazo[2,1-*b*][1,3,4]thiazol-5 amine (4a):** Yellow solid (98%), Mp 174-176 °C, IR (4000-600

cm^{-1}): ν_{max} = 3431 (stretch NH), 1642 (stretch C=N), 1559 (bend NH), 1412, 1339 (stretch C-N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H (ppm) 8.10-8.15 (m, 2H), 7.85-7.92 (m, 2H), 7.47-7.55 (m, 3H), 7.40 (m, 2H), 7.22-7.28 (m, 1H), 3.16 (brs, NH), 1.20 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 167.1, 160.5, 140.8, 138.4, 135.1, 133.6, 131.5, 130.7, 130.4, 129.3, 128.2, 127.7, 126.9, 56.3, 30.3. HR-MS (ESI) for $C_{20}H_{20}N_4S$ m/z calcd.: 349.1481; found: 349.1516 $[M + H]^+$.

***N–tert*-Butyl–6(4-methoxyphenyl)-2-phenylimidazo[2,1-*b*][1,3,4]thiazol-5-amine (4b):** Yellow solid (90%), Mp 212-213 °C, IR (4000-600 cm^{-1}): ν_{max} = 3411 (stretch NH), 1645 (stretch C=N), 1562 (bend NH), 1509, 1406, 1339 (stretch C-N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) 8.06 (d, 2H, *J* = 8.5 Hz), 7.83-7.91 (m, 2H), 7.46-7.54 (m, 3H), 6.94 (d, 2H, *J* = 8 Hz), 3.85 (s, 3H), 3.10 (brs, 1H), 2.17 (brs, enaminic proton), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz): δc (ppm) 160.0, 158.5, 140.6, 138.3, 131.4, 130.7, 129.2, 128.1, 127.8, 126.7, 125.8, 113.6, 56.1, 55.2, 30.3. HR-MS (ESI) for $C_{21}H_{22}N_4OS$ m/z calcd.: 379.1587; found: 379.1580 $[M + H]^+$.

***N–tert*-Butyl-2-(4-chlorophenyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiazol-5-amine (4c):** Yellow solid (91%), Mp 219-221 °C, IR (4000-600 cm^{-1}): ν_{max} = 3437 (stretch NH), 1639 (stretch C=N), 1559 (bend NH), 1409, 1336 (stretch C-N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) 8.11 (d, 2H, *J* = 10 Hz), 7.82 (d, 2H, *J* = 10 Hz), 7.48 (d, 2H, *J* = 10 Hz), 7.40 (t, 2H, *J* = 10 Hz), 7.24-7.29 (m, 1H), 3.15 (brs, NH), 2.17 (brs, enaminic proton), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 159.2, 138.7, 137.7, 135.0, 129.6, 129.1, 128.3, 128.0, 127.0, 126.9, 126.81, 126.80, 56.4, 30.3. HR-MS (ESI) for $C_{20}H_{19}ClN_4S$ m/z calcd.: 383.1091; found: 383.1125 $[M + H]^+$.

***N-tert*-Butyl-2(4-chlorophenyl)-6-(4-nitrophenyl)imidazo[2,1-*b*][1,3,4]thiazol-5-amine (4d):** Yellow solid (90%), Mp 221-222 °C, IR (4000-600 cm^{-1}): ν_{max} = 3434 (stretch NH), 2952 (sp^2 -CH), 2919 (sp^3-CH), 1592 (stretch C=N), 1509 (asymm. stretch NO_2), 1468 (symm. stretch NO_2), 1327 (stretch C-N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H (ppm) 8.42 (d, 2H, *J* = 12 Hz), 8.24 (d, 2H, *J* = 8 Hz), 7.82 (d, 2H, *J* = 8 Hz), 7.51 (d, 2H, *J* = 12 Hz), 3.15 (brs, NH), 1.10 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 160.4, 160.4, 146.2, 141.6, 141.6, 138.2, 129.8, 128.7, 128.1, 127.0, 123.7, 57.0, 30.4. HR-MS (ESI) for $C_{20}H_{18}ClN_5O_2S$ m/z calcd.: 450.0761; found: 450.0750 $[M + Na]^+$.

***N*-(2,6-Dimethylphenyl)-2,6-diphenylimidazo[2,1-*b*][1,3,4]thiazol-5-amine (4e):** Yellow solid (87%), Mp 194-195 °C, IR (4000-600 cm^{-1}): ν_{max} = 3417 (stretch NH), 1642 (stretch C=N), 1559 (bend NH), 1409 (stretch C-N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) 8.02 (d, 2H, *J* = 8 Hz), 7.69 (d, 2H, *J* = 7 Hz), 7.41-7.51 (m, 3H), 7.36 (t, 2H, *J* = 7.5 Hz), 7.22-7.27 (m, 1H), 6.99 (d, 2H, *J* = 7.5 Hz), 6.853 (t, 1H, *J* = 7.5 Hz), 5.29 (brs, NH), 2.17 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 161.0, 140.7, 140.5, 136.2, 133.9, 131.5, 130.3, 129.1, 129.1, 128.3, 128.1, 126.9, 126.7, 126.1, 124.7, 122.1, 18.6. HR-MS (ESI) for $C_{24}H_{20}N_4S$ m/z calcd.: 397.1481; found: 397.1473 $[M + H]^+$.

***N*-Cyclohexyl-2,6-diphenylimidazo[2,1-*b*][1,3,4]thiazol-5-amine (4f):** Yellow solid (90%), Mp 211-213 °C, IR (4000-600 cm^{-1}): ν_{max} = 3437 (stretch NH), 1639 (stretch C=N), 1556 (bend NH), 1412, 1339 (stretch C-N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) 8.04 (d, 2H, *J* = 8 Hz), 7.86-7.92 (m, 2H), 7.48-7.54 (m, 3H), 7.42 (t, 2H, *J* = 8 Hz), 7.24-7.28 (m, 1H) (merge with $CDCl_3$ region (7.260), 3.24-3.40 (m, 2H), 1.92-2.05 (m, 2H), 1.68-1.78 (m, 2H), 1.58-1.62 (m, 1H), 1.15-1.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 160.9, 160.8, 134.8, 134.0, 131.6, 130.7, 129.3, 128.7, 128.6, 126.9, 126.6, 125.9, 56.8, 34.2, 25.9, 25.0. HR-MS (ESI) for $C_{22}H_{22}N_4S$ m/z calcd.: 375.1637; found: 375.1648 $[M + H]^+$.

***N-tert*-Butyl-6-(2-chloro-5-nitrophenyl)-2-(4-nitrophenyl) imidazo[2,1-*b*][1,3,4]thiadiazol-5-amine (4g):** Orange solid (85%), Mp 210-211 °C, IR (4000-600 cm^{-1}): ν_{max} = 3428 (stretch NH), 1642 (stretch C=N), 1559 (bend NH), 1412 (asymm. Stretch NO_2), 1341 (symm. stretch NO_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H (ppm) 8.55 (d, 1H, *J* = 2.4 Hz), 8.39 (dt, 2H, *J* = 8 Hz, *J* = 4 Hz), 8.17 (dd, 1H, *J* = 8 Hz, *J* = 4 Hz), 8.11 (dt, 2H, *J* = 8 Hz, J = 4 Hz), 7.65 (d, 1H, *J* = 8.8 Hz), 3.28 (brs, NH), 2.17 (brs, enaminic proton), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 158.9, 149.6, 139.6, 135.9, 135.5, 135.4, 135.3, 131.0, 129.2, 127.8, 127.6, 124.7, 123.7, 56.0, 30.0. HR-MS (ESI) for $C_{20}H_{17}ClN_6O_4S$ m/z calcd.: 495.0612; found: 473.0590 $[M + Na]^+$.

2-(4-Chlorophenyl)-*N*–(2,6-dimethylphenyl)-6-(4-methoxy phenyl)imidazo[2,1-*b*][1,3,4] thiazol-5-amine (4h): Yellow solid (85%), Mp 197-198 °C, IR (4000-600 cm^{-1}): ν_{max} = 3414 (stretch NH), 1642 (stretch C=N), 1559 (bend NH), 1412, 1339 (stretch C-N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H (ppm) 7.96 (d, 2H, *J* = 8 Hz), 7.62 (dt, 2H, *J* = 8 Hz, *J* = 4 Hz), 7.41 (dt, 2H, *J* = 8 Hz, *J* = 4 Hz), 6.99 (d, 2H, *J* = 8 Hz), 6.90 (d, 2H, *J* = 8 Hz), 6.84 (t, 1H, *J* = 8 Hz), 5.24 (brs, NH), 3.82 (s, 3H), 2.15 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 158.9, 137.7, 129.5, 129.3, 129.0, 127.9, 127.9, 127.9, 127.5, 122.1, 113.9, 55.3, 18.7. HR-MS (ESI) for $C_{25}H_{21}ClN_4OS$ m/z calcd.: 461.1197; found: 461.1210 $[M + H]^+$.

2,6-*bis*(4-Chlorophenyl)-*N*–cyclohexylimidazo[2,1-*b*][1,3,4] thiadiazol-5-amine (4i): Yellow solid (92%), Mp 223-224 °C, IR (4000-600 cm^{-1}): ν_{max} = 3437 (stretch NH), 1639 (stretch C=N), 1559 (bend NH), 1409, 1336 (stretch C-N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) 8.02 (d, 2H, *J* = 8.5 Hz), 7.82 (d, 2H, *J* = 8 Hz), 7.49 (d, 2H, *J* = 8.5 Hz), 7.37 (d, 2H, *J* = 8.5 Hz), 3.15-3.30 (m, 2H), 1.87-2.00 (m, 2H), 1.68-1.80 (m, 2H), 1.50-1.68 (m, 1H), 1.13-1.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δc (ppm) 159.7, 139.7, 137.7, 133.6, 133.1, 132.2, 126.6, 128.9, 128.6, 128.0, 127.1, 56.8, 33.9, 25.8, 24.8. HR-MS (ESI) for $C_{22}H_{20}Cl_2N_4S$ m/z calcd.: 465.0677; found: 465.0653 $[M + Na]^+$.

***N-tert*-Butyl-6-(4-methoxyphenyl)-2-(4-nitrophenyl)imidazo [2,1-*b*][1,3,4]thiadiazol-5-amine (4j):** Red solid (92%), Mp 210-211 °C, IR (4000-600 cm^{-1}): ν_{max} = 3431 (stretch NH), 1645 (stretch C=N), 1562 (asymm. stretch NO_2), 1415 (symm. stretch NO_2), 1338 (stretch C-N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H (ppm)

8.34-8.38 (m, 2H), 8.03-8.08 (m, 4H), 6.92-6.97 (m, 2H), 3.85 (s, 3H), 3.11 (brs, NH), 2.17 (brs, 1H), 1.20 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz): δc (ppm) 158.9, 157.2, 149.2, 140.6, 139.4, 136.4, 128.2, 127.5, 127.3, 126.1, 124.6, 113.7, 56.3, 55.3, 30.4. HR-MS (ESI) for $C_{21}H_{21}N_5O_3S$ m/z calcd.: 424.1438; found: 424.1463 $[M + H]^+$.

2-(4-Chlorophenyl)-*N*-cyclohexyl-6-phenylimidazo[2,1-*b*] [1,3,4]thiazol-5-amine (4k): Yellow solid (91%), Mp 201-202 °C, IR (4000-600 cm^{-1}): ν_{max} = 3423 (stretch NH), 1642 (stretch C=N), 1559 (bend NH),1415, 1336 (stretch C-N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) 8.03 (d, 2H, *J* = 7.5 Hz), 7.83 (d, 2H, *J* = 8.5 Hz), 7.49 (d, 2H, *J* = 8.5 Hz), 7.42 (t, 2H, *J* = 7.5 Hz), 7.24-7.28 (m, 1H), 3.23-3.36 (m, 2H), 2.170 (s, enaminic proton), 1.91-2.02 (m, 2H), 1.69-1.77 (m, 2H), 1.15-1.35 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 169.7, 169.6, 134.7, 129.6, 129.1, 129.1, 128.9, 128.0, 126.7, 125.9, 125.9, 125.9, 56.8, 51.0, 34.2, 25.8, 24.8. HR-MS (ESI) for $C_{22}H_{21}ClN_4S$ m/z calcd.: 409.1248; found = 409.1225 $[M + H]^+$.

***N*-(2,6-Dimethylphenyl)-2,6-bis(4-nitrophenyl)imidazo[2,1-*b*][1,3,4]thiazol-5-amine (4l):** Brown solid (85%), Mp 180-181 °C, IR (4000-600 cm^{-1}): ν_{max} = 3434 (stretch NH), 1639 (stretch CN), 1553 (asymm. stretch NO_2), 1409 (symm. stretch NO_2), 1341 (stretch C-N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) 8.32 (d, 2H, *J* = 8.4 Hz), 8.21 (d, 2H, *J* = 8.8 Hz), 8.17 (d, 2H, *J* = 8.6 Hz), 7.85 (d, 2H, *J* = 8.4 Hz), 7.04 (d, 2H, *J* = 7.4 Hz), 6.94 (t, 1H, *J* = 7.3 Hz), 5.41 (brs, NH), 2.17 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 149.5, 146.2, 140.7, 140.1, 139.4, 139.4, 135.6, 129.3, 129.3, 127.6, 127.6, 126.3, 124.6, 123.9, 123.7, 18.7. Anal. Calcd. for $C_{24}H_{18}N_6O_4S$; C, 59.25; H, 3.73; N, 17.27. Found: C, 59.29; H, 3.81; N, 17.31.

2-(4-Chlorophenyl)-*N*-cyclohexyl-6-(4-methoxyphenyl) imidazo[2,1-*b*][1,3,4]thiazol-5-amine (4m): Yellow solid (86%), Mp 208-209 °C, IR (4000-600 cm^{-1}): ν_{max} = 3428 (stretch NH), 1636 (stretch C=N), 1565 (bend NH), 1409 (stretch C-N). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) 7.98 (d, 2H, *J* = 9 Hz), 7.82 (d, 2H, *J* = 8.5 Hz), 7.48 (d, 2H, *J* = 8.5 Hz), 6.97 (d, 2H, *J* = 9 Hz), 3.85 (s, 3H), 3.18-3.27 (bm, 2H), 1.92-1.98 (m, 2H), 1.71-1.78 (m, 2H), 1.17-1.33 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 177.8, 177.8, 177.5, 161.6, 157.3, 142.0, 129.5, 127.9, 127.2, 113.9, 113.9, 113.9, 55.3, 55.3, 34.0, 25.8, 24.8. HR-MS (ESI) for $C_{23}H_{23}ClN_4OS$ m/z calcd.: 461.1173; found: 461.1136 $[M + Na]^+$.

***N*-*tert*-Butyl-2-(4-chlorophenyl)-6-(4-methoxyphenyl)imidazo [2,1-*b*][1,3,4]thiazol-5-amine (4n):** Off white solid (85%), Mp 209-210 °C, IR (4000-600 cm^{-1}): ν_{max} = 3428 (stretch NH), 1642 (stretch C=N), 1562 (bend NH), 1415, 1336 (stretch C-N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H (ppm) 8.05 (dt, 2H, *J* = 8 Hz, *J* = 4 Hz), 7.81 (dt, 2H, *J* = 8 Hz, *J* = 4 Hz), 7.48 (dt, 2H, *J* = 8 Hz, *J* = 4 Hz), 6.94 (dt, 2H, *J* = 8 Hz, *J* = 4 Hz), 3.85 (s, 3H), 3.09 (brs, NH), 2.18 (brs, enaminic proton), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 158.7, 137.5, 137.5, 129.6, 129.2, 128.1, 127.9, 127.7, 127.7, 113.7, 56.2, 55.3, 30.4. Anal. Calcd. for $C_{21}H_{21}ClN_4OS$; C, 61.08; H, 5.13; N, 13.57. Found: C, 61.13; H, 5.18; N, 13.63.

***N*-*tert*-Butyl-2(4-methoxyphenyl)-6-phenylimidazo[2,1-*b*] [1,3,4]thiadiazol-5-amine (4o):** Off white solid (85%), Mp 204-204.5 °C, IR (4000-600 cm^{-1}): ν_{max}= 3443 (stretch NH), 1640 (stretch C=N), 1563 (bend NH), 1467 (stretch C-N), 1414 (stretch C-N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H (ppm) 8.10 (d, 2H, *J* = 8 Hz), 7.80 (d, 2H, *J* = 8.8 Hz), 7.38 (t, 2H, *J* = 8 Hz), 7.22-7.26 (m, 1H), 6.99 (d, 2H, *J* = 8.8 Hz), 3.87 (s, 3H), 3.13 (brs, NH), 1.18 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 162.3, 160.4, 135.2, 135.2, 128.4, 128.2, 128.2, 126.8, 126.8, 126.8, 123.3, 114.7, 56.3, 55.6, 30.3. Anal. Calcd. for $C_{21}H_{22}N_4OS$; C, 66.64; H, 5.86; N, 14.80. Found: C, 66.70; H, 5.80; N, 14.86.

***N*-*tert*-Butyl-2(4-methoxyphenyl)-6-(4-nitrophenyl)imidazo [2,1-*b*][1,3,4]thiadiazol-5-amine (4p):** Yellow solid (87%), Mp 227-227.5 °C, IR (4000-600 cm^{-1}): ν_{max}= 3447 (stretch NH), 1643 (stretch C=N), 1567 (bend NH), 1412 (stretch C-N), 1340 (stretch C-N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H (ppm) 8.40 (d, 2H, *J* = 8 Hz), 8.22 (d, 2H, *J* = 8 Hz), 7.80 (d, 2H, *J* = 8 Hz), 7.00 (d, 2H, *J* = 8 Hz), 3.88 (s, 3H), 3.14 (brs, NH), 2.16 (s, enaminic proton), 1.20 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 162.6, 146.0, 141.9, 136.0, 128.6, 128.5, 126.8, 123.7, 122.8, 122.8, 114.8, 57.0, 55.7, 30.4. Anal. Calcd. for $C_{21}H_{21}N_5O_3S$; C, 59.56; H, 5.00; N, 16.54. Found: C, 59.65; H, 5.08; N, 16.61.

***N*-*tert*-Butyl-6-(4-fluorophenyl)-2-phenylimidazo[2,1-*b*][1,3,4] thiadiazol-5-amine (4q):** Yellow solid (89%), Mp 233.7-233.9 °C, IR (4000-600 cm^{-1}): ν_{max} = 3446 (stretch NH), 1639 (stretch C=N) , 1559 (bend NH), 1360 (stretch C-N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H (ppm) 8.09-8.16 (m, 2H), 7.83-7.90 (m, 2H), 7.46-7.53 (m, 3H), 7.06 (t, 2H, *J* = 8 Hz), 3.07 (brs, NH), 2.16 (s, enaminic proton), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 163.1, 160.7, 160.6, 131.6, 131.2, 131.2, 130.6, 130.2, 129.3, 129.1, 128.6, 128.5, 127.1, 126.8, 115.2, 115.0, 56.3, 30.3. Anal. Calcd. for $C_{20}H_{19}FN_4S$; C, 65.55; H, 5.23; N, 15.29. Found: C, 65.62; H, 5.32; N, 15.35.

***N*-*tert*-Butyl-2-(4-chlorophenyl)-6-(4-fluorophenyl)imidazo [2,1-*b*][1,3,4]thiadiazol-5-amine (4r):** Yellow solid (86%), Mp 229.0-229.2 °C, IR (4000-600 cm^{-1}): ν_{max} = 3431(stretch NH), 1648 (stretch C=N), 1564 (bend NH), 1349(stretch C-N). ^{1}H NMR ($CDCl_3$, 400 MHz): δH (ppm) 8.09-8.15 (m, 2H), 7.80 (d, 2H, *J* = 8.8 Hz), 7.47 (d, 2H, *J* = 8.4 Hz), 7.07 (t, 2H, *J* = 8.8 Hz), 3.07 (brs, NH), 2.17 (s, enaminic proton), 1.18 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 163.2, 160.7, 159.3, 140.7, 137.7, 131.1, 131.1, 129.6, 129.1, 128.6, 128.5, 128.0, 115.2, 115.0, 56.4, 30.3. Anal. Calcd. for $C_{20}H_{18}ClFN_4S$; C, 59.92; H, 4.53; N, 13.98. Found: C, 59.99; H, 4.62; N, 14.06.

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