Eco-Friendly Synthesis of water-soluble Imidazole Derivatives: Exploring Multiple Pathways and Their Catalytic Properties

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Abstract: In this study, we report the synthesis of water-soluble imidazole derivatives featuring base-sensitive fluorophore peripheral units. The synthesis was carried out using various organic compounds through conventional methods, as well as silica-supported Muffle furnace and microwave techniques. Our findings indicate that the solvent-free synthetic approach offers significant advantages over conventional methods. These advantages include non-toxic reagents, markedly reduced reaction times, straightforward workup procedures without the need for extensive purification, and higher yields. Moreover, the synthesized substituted imidazole derivatives demonstrated excellent catalytic activity in the preparation of Gembisamide derivatives when employing the conventional synthetic approach. This highlights the potential of these derivatives in various catalytic applications.

Keywords: Imidazole, Grinding method, Muffle Furnace, Microwave, Solid phase, Different solvent, Optimization.

Introduction

In Summary recently, nitrogen-containing aromatic heterocyclic compounds, particularly imidazoles, have garnered significant attention in research and industrial chemistry in recent years, mainly due to their versatile range of biological and pharmacological activities carbon materials is probably the good alternative for the genetic-ration of various organic and bioorganic compound synthesis. Why because, they have extraordinary properties and applications for the good example, huge explicit surface covering area, high permeable and semi-permeable structure and solid connections among the C and H atoms. Thus, graphene (C70H26O11) oxide is a promising candidate for a diverse range of catalytic applications. They play a pivotal main role in the synthesized of biologically activing molecules, atom, particles and process such as anticancer, anti-aging, anticoagulant, anti-inflammatory, antimicrobial, anti-tubercular, antidiabetic, antimalarial, antiviral drugs, and enzyme inhibitors.[1,2] They also act as Stereo selective and stereo specific plant treatment and growth regulators, fungicides, herbicides, and therapeutic agents. Nowadays, greener chemistry and organometallic catalytic have extended the application of pyridinium, pyrazine, imidazoles as different kind of ionic liquids and poly ionic liquids N-heterocyclic C (NHCs) catalytic response[3,] As a result, imidazole salts and their various derivatives have gained popularity due to the increasing demand for eco-friendly methods in novel organic synthesis.

There are several approaches for the synthesis of substituted imidazoles by condensation, ring cyclization oxidation conversion, solid face analysis, flash vacuum pyrolysis microreactor and ionic liquid promoted technique. Some of the well-known methods for the synthesis of substituted imidazoles are Van Leusen Debus-Radziszewski, Marckwald and Wallach in the last few decades. Continuing our interest in *N*-containing heterocycles.[4,5] They play a pivotal role in the synthesis of biologically active molecules. In most cases, tri and tetra-substituted imidazoles are synthesized by three or four components of cyclocondensation of 1,2-diketones, ammonium acetate with aldehydes, and anilines using a variety of different catalysts under efficient green method or solvent-based conditions. We propose this review, which comprehensively explores recent advancements in imidazole synthesis. We emphasize reviewing critical strategies, catalytic approaches, and sustainable methodologies based on two, three, and four components. As imidazole derivative synthesis

continues to evolve, it promises scientific innovation while addressing environmental sustainability concerns in the chemical industry, Green approaches for the synthesis of poly-functionalized imidazole derivatives: a comprehensive review, Geetika Patel, Devendra Kumar Dewangan, Nikita Bhakat, Subhash Banerjee, [6] Synthesis of imidazole derivatives in the last 5 years: An update[7] Such as anticancer, antiaging, anticoagulant, anti-inflammatory, antimicrobial, Antitubercular, antidiabetic, antimalarial, antiviral drugs and enzyme inhibitors[8] Ring cyclization[9] Continuing our interest in *N*-containing heterocycles, [10,11] Imidazole and pyridinium synthesis, Functionalization and Physicochemical Properties of a Privileged structure system in Medicinal part of Chemistry[12] This is the synthesis part of despite producing relatively low periodic percentage of yields is still used to creativity the C-different substituted imidazoles and pyridinium among the *N*-based heterocyclic compounds. Imidazole 1 plays a very important role in humans.

The substance plays a significant role in various scientific fields, including chemical sciences, biological sciences, and materials science. It is utilized as a catalyst in compound synthesis and is crucial in the development of new pharmaceuticals,[13]

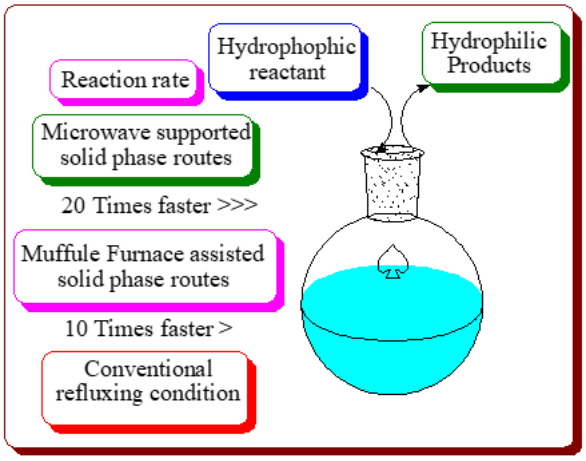
A recent study conducted by Movellan and collaborators highlights this significant effect[14]

Furthermore, disubstituted imidazoles featuring a carbomethoxy group 31 at the C-4 position can be synthesized through the coupling of functionalized amidoximes 32 and methyl propiolate 33. This reaction occurs in the presence of a catalytic amount of 1,4-diazabicyclo[2.2]octane (DABCO) under microwave irradiation[15].

On the other hand, o, m, and ptrisubstituted imidazoles 36 can be synthesized using o, m-dioxo-o-substituted propanoates 37 as precursors. This is achieved through condensation with $NH_4CH_3CO_2$ and various benzaldehydes 38 in a mixture of ethanol and acetic acid as catalysts at room temperature[16]

o-Aryl-*m,p*-dicarbonitrile imidazole derivatives 39 could be obtained from the coupling of substituted aromatic aldehydes 40 and 2,3-diaminomaleonitriles 41 in the presence of a mixture of cerium (IV) ammonium nitrate/HNO_3 (CAN: NA|0.05: 0.4 Equiv.) at 120 ^{0}C, for less than 1 hours without using solvents Kalhor[17].

Show the use of different substituted 1, 2-diphenylethane1, 2-dione (benzyl) 48, different substituted -CHO 49 and $NH_4CH_3CO_2$ under various conditions, with the aim of optimizing the construction of *o, m, p*-trisubstituted imidazole 50 with great structural diversity [18, 19, 20, 21]

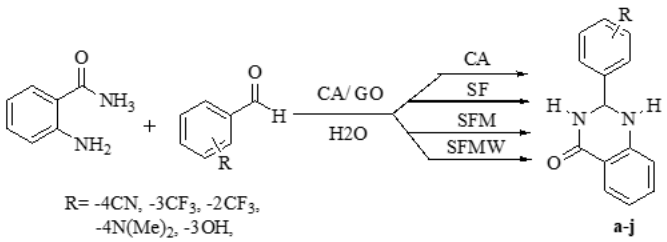


Results and Discussion synthesis of imidazole derivatives

In a recent experiment, a mixture containing 0.005 g of an organo catalyst was prepared alongside 2-aminobenzamide (1 mmol) and stirred at 30 ºC for 10 minutes. Following this initial period, various substituted benzaldehydes (1.2 mmol) were added to the reaction mixture.

The resulting solution was continuously stirred at the same temperature until the reaction was deemed complete. Once the reaction was finished, the catalyst was separated from the mixture using normal filtration. The organic phase, enriched with the target product, was then concentrated under reduced pressure. Finally, the crude product mixture underwent purification through column chromatography to isolate the desired compounds.(**Scheme-I**).

In the present study, citric acid-extracted modified graphene oxide ($C_{70}H_{26}O_{11}$) was synthesized and utilized as a heterogeneous nanocatalyst for the efficient production of imidazole and pyridinium derivatives. This reaction was conducted under mild conditions and required a short reaction time. The modified graphene oxide was prepared using a modified Hummers method, followed by the covalent bonding of citric acid to the graphene oxide nanosheets. Various analytical techniques were employed to characterize the resulting material, confirming its structure and catalytic properties.



Conventional Approach (CA): Water/CA: rt, 10-75 min, 87-95%; Solvent Free Grinding Method (SF): 25 min, 88%; Solvent Free Muffle Furnace (SFM): Silica gel 100 ^{0}C, 17 min, 90%; Solvent Free Microwave Reaction (SFMW): 5 min, 98%

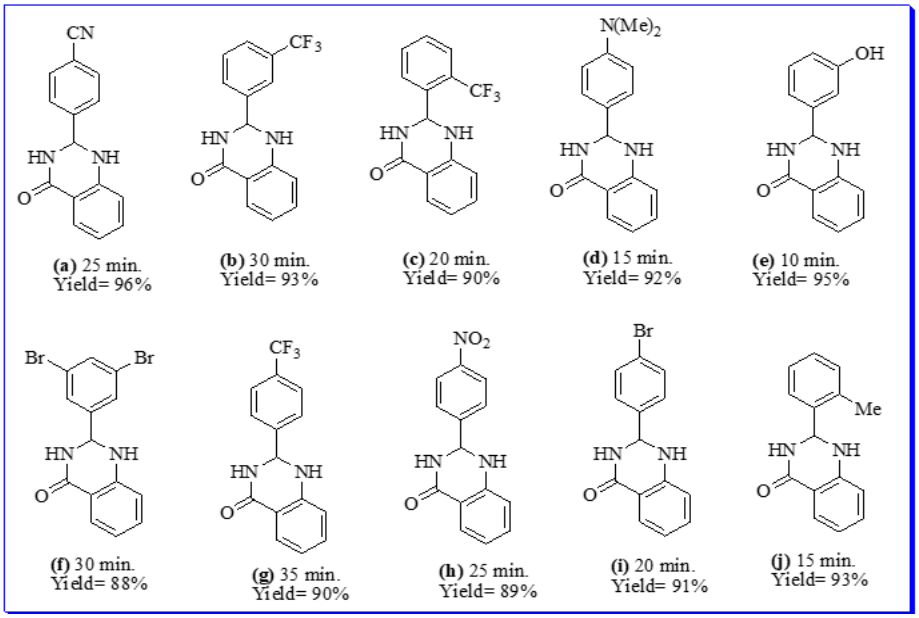
Scheme 1: One-pot synthesis of substituted gem-bisamides derivatives under multiple routes.

S.No	Catalytic Activity	Imidazole derivatives for different concentration											
		1.8135 × 10^{-2} mmol				3.627 × 10^{-2} mmol				5.440 × 10^{-2} mmol			
		CR		MR		CR		MR		CR		MR	
		Time	%	Time	%	Time	%	Time	%	Time	%	Time	%
1	a	90	66	45	77	80	76	35	83	90	89	25	96
2	b	100	65	50	74	90	75	40	80	89	88	30	93
3	c	80	67	40	76	70	77	30	82	91	92	20	90
4	d	70	74	35	80	60	84	25	85	50	91	15	92
5	e	60	77	30	79	50	87	20	86	40	90	10	95
6	f	100	62	50	75	90	72	40	81	80	93	30	88
7	g	110	64	55	72	100	74	45	81	90	91	35	90
8	h	90	67	45	73	80	77	35	80	70	92	25	89
9	i	80	69	40	79	70	79	30	83	60	91	20	91
10	j	70	72	35	76	60	82	25	84	50	95	15	93
No Even after change 5 h. appreciable reaction.													

Table-1 Different Concentration for Imidazole derivative reaction.

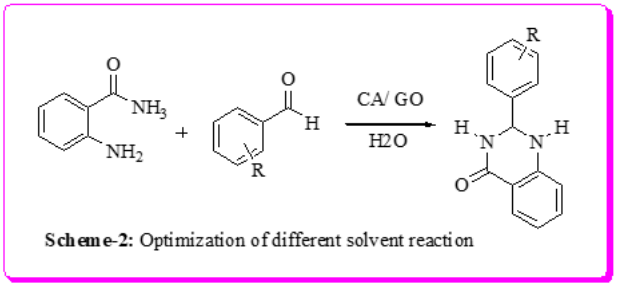
S.No	Using for different solvent	Catalytic activity loading (Mg)	Yield of (%)
1	H_2O	10	98
2	CH_3CH_2OH	10	77
3	CH_3CH_2OH: H_2O	10	73
4	CH_3OH: H_2O	10	57
5	CH_3OH	10	53
6	THF	10	52
7	Isopropyl alcohol	10	72
8	Toluene	10	68
9	1,4-Dioxane	10	15
10	Ethyl Acetate	10	70
11	Acetonitrile	10	68
[a]**Using for different solvent reaction conditions:** *o*-Aminobenzamide (1 mmol), aldehydes (1.2 mmol), GO/CA catalytic activity for (0.005 g), solvent (5 mL), 30 min. at room temperature; [b]All are isolated yield.			

Table-2 Different using solvent reaction.



Optimization of Solvent

In the order to identical a reliable solvent for the synthesized heterogeneous nanocatalytic activity in the different substituted imidazole derivatives synthesis, a order of solventsuch as CH_3CH_2OH, CH_3OH, isopropanol, CH_3CN, THF, 1,4-dioxane, $PhCH_3$, CH_3CH_2OH:H_2O, CH_3OH: H_2O and H_2O were employed. **(Scheme-2)**



Scheme-2: Optimization of different solvent reaction

To develop more benign live ofthe carbocatalytic activity and practice greener approach protocols, the chemistry experiment was tried H_2O as medium, the results were encouraging and good yield were observed up to 98% yield. Without further anypurification. Finally H_2O medium at room temperature. This chemical reaction was performedusing different organic solvents and the desired different type imidazoles derivative with a good yield upto 85% **(Table-1).**

Catalytic Activity

Conventional and solid phase solvent free Muffle furnace methods are used to make different type imidazole derivatives from readily available starting materials. In the presence of various concentrations of our catalyst with/without solvent, a one-pot multicomponent reaction is tested. Substituted imidazole derivatives which outperformed the other different type imidazole derivatives in the terms and condition of catalytic response. For one-pot preparation of substituted oxazinone derivatives, the reactions are repeated with various.

Concentrations such as 1.813×10^{-2} mmol, 3.627×10^{-2} mmol, 5.440×10^{-2} mmol, and 7.254×10^{-2} mmol to optimize the catalyst concentration of core moiety containing imidazole derivatives. As the catalyst concentration is increased from 5.440×10^{-2} mmol into 7.254×10^{-2} mmol, the proportion of yield and reaction. time have not changed significantly. Under a conventional/solid phase technique, various substituted oxazinone derivatives are produced; reactions are repeated with varying concentrations. $MgFe_2O_4$ and SiO_2-SO_3H catalysts were utilised to prepare benzthioxazione under microwave aided solvent free method, as shown in **(Tables-2).** The low reaction time and higher yield. The yield of percentage is significant, but the catalyst is expensive, as is the base sensive catalyst. The gem-bisamides but derivatives were synthesised using 200 mg of Amberlite IRA-400 Cl catalyst; this took over 2 h. Complete. Imidazole derivatives take 20 minutes to complete. Catalyst has potential due to its faster reaction time, huge of the yield. The need of solvents, and

environmental friendliness. **(Table-1.)** Derivatives are synthesised with the use of varied concentrations of Imidazole **(a-j).** T= Time in minutes; Y= percentage of yield

Conclusions

In summary, citric acid was successfully synthesized on graphene nanosheets through a straightforward chemical modification method. Imidazole derivatives were efficiently produced using metal-free citric acid-modified graphene nanosheets under mild conditions. Surface analysis of the prepared heterogeneous organocatalyst confirmed effective functionalization of the graphene oxide with citric acid. The resulting citric acid-grafted graphene oxide demonstrated enhanced acidic properties and remarkable catalytic activity, showcasing significant stability and sustainability even after multiple reaction cycles.

Conflict of Interest

The authors declare that there is no any further conflict of interests regards to the further article publication of this journal.

Supporting Information

Elemental supporting further procedure, all the spectral and analytical data are available in the supporting information.

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Experimental

Analytical reagent grade graphite powder, sodium nitrate,potassium permanganate, citric acid and hydrogen peroxide (30%) were purchased from Sigma-Aldrich and used withoutfurther purifications.

Synthesis of heterogeneous organ catalyst

Grapheneoxide (GO) was synthesized from graphite powder using modifiedHummers method then citric acid modified graphene oxidewas synthesized by the following procedure, 200 mg of graphene oxide was dispersed in 50 mL of water *via* sonication. To a dispersed solution, 50 mL of 10M citric acid solution were added dropwise with constant stirring. The resultant solution was stirred at room temperature for 3 h and the obtainedblack precipitate was washed thoroughly and labeled as CA/GO.

***2-(4-cyanophenyl)-2,3-dihydroquinazolin-4(1H)-one (a)*:** Yield:95%; solid, m.p. 175-177 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hd, 7.20-7.27), (1Hd, 7.15-7.22), (1Ht, 6.05), (1Hd, 6.31), (1Hd, 8.65), (1Hd, 7.05), (1Ht, 7.47), (1Ht, 6.85), (1Hd, 7.69); ^{13}C NMR (75 MHz, DMSO) δ: 76.0, 113.6, 116.7, 117.2, 125.9, 126.7, 128.3, 132.9, 144.4, 145.6, 165. MS*: m/z*: 224.26; Anal. Calculated for $C_{14}H_{12}N_2O$: C, 74.91; H, 5.35; N, 12.48; Found: C, 74.87; H, 5.31; N, 12.44.

***2-(3-trifluoromethanephenyl)-2,3-dihydroquinazolin-4(1H)-one (b)*:** Yield: 85%; solid, m.p. 165-167 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hd, 7.20-7.27), (1Hd, 7.15-7.22), (1Ht, 6.05), (1Hd, 6.31), (1Hd, 8.65), (1Hd, 7.05), (1Ht, 7.47), (1Ht, 6.85), (1Hd, 7.69); ^{13}C NMR (75 MHz, DMSO) δ: 76.3, 113.7, 116.9, 117.3, 125.5, 126.5, 128.7, 132.3, 144.7, 145.7, and 165.3. MS*: m/z*: 224.26; Anal. Calculated for $C_{14}H_{12}N_2O$: C, 74.91; H, 5.35; N, 12.48; Found: C, 74.86; H, 5.30; N, 12.87.

***2-(2-trifluoromethanephenyl)-2,3-dihydroquinazolin-4(1H)-one (c)*:** Yield: 80%; solid, m.p. 164-166 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hd, 7.63-7.69), (1Hm, 7.71-7.7.79), (1Hm, 7.10-7.19), (1Hd, 7.29), (1Hd, 6.05), (1Hd, 6.27), (1Hd, 8.65), (1Hd, 7.00), (1Hm, 7.47), (1Hm, 6.85), (1Hd, 7.67); ^{13}C NMR (75 MHz, DMSO) δ: 69.3, 113.4, 115.3, 116.8, 117.1, 124.1, 128.2, 128.4, 129.3, 132.7, 145.5, 159.4, 165.1. MS*: m/z*: 224.26; Anal. Calculated for $C_{14}H_{12}N_2O$: C, 74.91; H, 5.35; N, 12.48; Found: C, 74.85; H, 5.29; N, 12.42.

***7-Bromo-2-(4-N-dimethylphenyl)-2,3-dihydroquinazolin-4(1H)-one (d)*:** Yield: 78%; solid, m.p. 164-166 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (3Hs, 3.81), (1Hd, 6.89-6.97), (1Hd, 7.45-7.54), (1Hd, 6.01), (1Hd, 6.31), (1Hd, 8.65), (1Hd, 7.05), (1Hm, 7.47), (1Hm, 6.80), (1Hd, 7.67); ^{13}C NMR (75 MHz, DMSO) δ: 55.9, 76.1, 113.5, 114.1, 116.3, 117.3, 127.8, 128.1, 132.8, 136.5, 145.3, 158.1, 165.7. MS*: m/z*: 254.29; Anal. Calculated for $C_{15}H_{14}N_2O_2$: C, 70.78; H, 5.50; N, 11.01; Found: C, 70.74; H, 5.46; N, 10.97.

***2-(3-Hydroxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (e)*:** Yield: 75%; solid, m.p. 160-162 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (3Hs, 3.75), (1Hs, 6.95), (1Hd, 6.91-6.97), (1Hd, 7.11), (1Hd, 6.05), (1Hd, 6.27), (1Hd, 8.65), (1Hd, 7.05) (1Hd, 7.69), (1Hm, 7.27), (1Hm, 7.47), (1Hm, 6.85); ^{13}C NMR (75 MHz, DMSO) δ: 55.5, 76.4, 111.1, 112.3, 113.5, 116.5 117.2, 118.2, 128.5, 129.3, 132.7, 145.5, 145.7, 160.7, 165.9. MS*: m/z*: 254.29; Anal. Calculated for $C_{15}H_{14}N_2O_2$: C, 70.78; H, 5.50; N, 11.01; Found: C, 70.73; H, 5.42; N, 10.92.

***2-(3,5-dibromophenyl)-2,3-dihydroquinazolin-4(1H)-one (f)*:** Yield: 76%; solid, m.p. 169-171 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hs, 7.45), (1Hd, 7.54), (1Hd, 7.37), (1Hd, 6.05), (1Hd, 6.21), (1Hd, 8.65), (1Hd, 7.01), (1Hd, 7.68), (1Hm, 7.28) (1Hm, 7.47), (1Hm, 6.78); ^{13}C NMR (75 MHz, DMSO) δ: 75.5, 113.6, 116.9, 117.3, 122.8, 124.5, 128.2, 129.1, 129.6, 130.5, 132.8, 145.7, 146.3, 165.4. MS*: m/z*: 303.16; Anal. Calculated for $C_{14}H_{11}BrN_2O$: C, 55.41; H, 3.62; N, 9.23; Found: C, 55.37; H, 3.58; N, 9.19.

***2-(4-trifluoromethanephenyl)-2,3-dihydroquinazolin-4(1H)-one (g)*:** Yield: 74%; solid, m.p. 159-161 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hd, 7.55), (1Hd, 7.19), (1Hd, 6.05), (1Hd, 6.27), (1Hd, 8.65), (1Hd, 7.05), (1Hd, 7.69), (1Hm, 7.07), (1Hm, 7.25) (1Hm, 7.35), (1Hm, 6.79); ^{13}C NMR (75 MHz, DMSO) δ: 72.5, 111.3, 113.6, 116.7, 121.9, 127.5, 128.3, 128.9, 129.2, 132.5, 132.9, 136.3, 145.6, 165.3. MS*: m/z*: 303.16; Anal. Calculated for $C_{14}H_{11}BrN_2O$: C, 55.41; H, 3.62; N, 9.23; Found: C, 55.37; H, 3.58; N, 9.19.

***2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (h)*:** Yield: 88%; solid, m.p. 166-168 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hs, 7.47), (1Hd, 7.39), (1Hd, 7.33), (1Hd, 6.09), (1Hd, 6.31), (1Hd, 8.65), (1Hd, 7.07), (1Hd, 7.68), (1Hm, 7.29) (1Hm, 7.47), (1Hm, 6.80); ^{13}C NMR (75 MHz, DMSO) δ: 75.9, 113.8, 116.1, 117.3, 124.1, 126.5, 126.2, 128.3, 129.3, 132.7, 134.5, 145.6, 165.4. MS*: m/z*: 258.71; Anal. Calculated for $C_{14}H_{11}ClN_2O$: C, 64.93; H, 4.25; N, 10.82; Found: C, 64.89; H, 4.21; N, 10.78.

***2-(4-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (i)*:** Yield: 74%; solid, m.p. 159-161 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hd, 7.65), (1Hd, 7.24), (1Hd, 6.07), (1Hd, 6.08), (1Hd, 8.61), (1Hd, 7.05), (1Hd, 7.65), (1Hm, 7.21), (1Hm, 7.26) (1Hm, 7.41), (1Hm, 6.73); ^{13}C NMR (75 MHz, DMSO) δ: 70.5, 113.4, 116.7, 117.1, 126.5, 128.2, 128.3, 128.7, 132.6, 13.5, 132.9, 142.7, 145.3, 165.4. MS*: m/z*: 258.71; Anal. Calculated for $C_{14}H_{11}ClN_2O$: C, 64.93; H, 4.25; N, 10.82; Found: C, 64.87; H, 4.21; N, 10.78.

***2-(2-methylphenyl)-2,3-dihydroquinazolin-4(1H)-one (j)*:** Yield: 79%; solid, m.p. 189-191 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hs, 7.85), (1Hd, 7.79), (1Hd, 7.47), (1Hd, 6.05), (1Hd, 6.21), (1Hd, 8.65), (1Hd, 7.01), (1Hd, 7.68), (1Hm, 7.28) (1Hm, 7.47), (1Hm, 6.78); ^{13}C NMR (75 MHz, DMSO) δ: 75.5, 113.6, 116.9, 117.3, 122.8, 124.5, 128.2, 129.1, 129.6, 130.5, 132.8, 145.7, 146.3, 165.4. MS*: m/z*: 350.16; Anal. Calculated for $C_{14}H_{11}IN_2O$: C, 47.97; H, 3.14; N, 7.99; Found: C, 47.93; H, 3.10; N, 9.15.

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