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"MICROWAVE ASSISTED SOLVENT FREE SYNTHESIS 3-ARYL-1H-PYRAZOL-5-AMINES FROM BENZOYLACETONITRILE AND ITS REACTIONS."

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ABSTRACT
Synthesis of a series of 3-aryl-1*H*-pyrazol-5-amines from benzoylacetonitrile under microwave irradiation and their exploration are described in the present article. The benzoylacetonitrile are irradiated under microwave with hydrazine hydrate at 80 °C for 10 min. to afford desired 3-aryl-1*H*-pyrazol-5-amines. 3-phenyl-1*H*-pyrazol-5-amine subsequently treated with substituted aromatic aldehydes to afford corresponding substituted (E)-N-benzylidene-3-phenyl-1*H*-pyrazol-5-amine which on treatment with diversified sulfonyl chloride followed by reduction in presence of sodium borohydride to afford 1-sulfonated N-benzyl-3-phenyl-1*H*-pyrazol-5-amines derivatives.

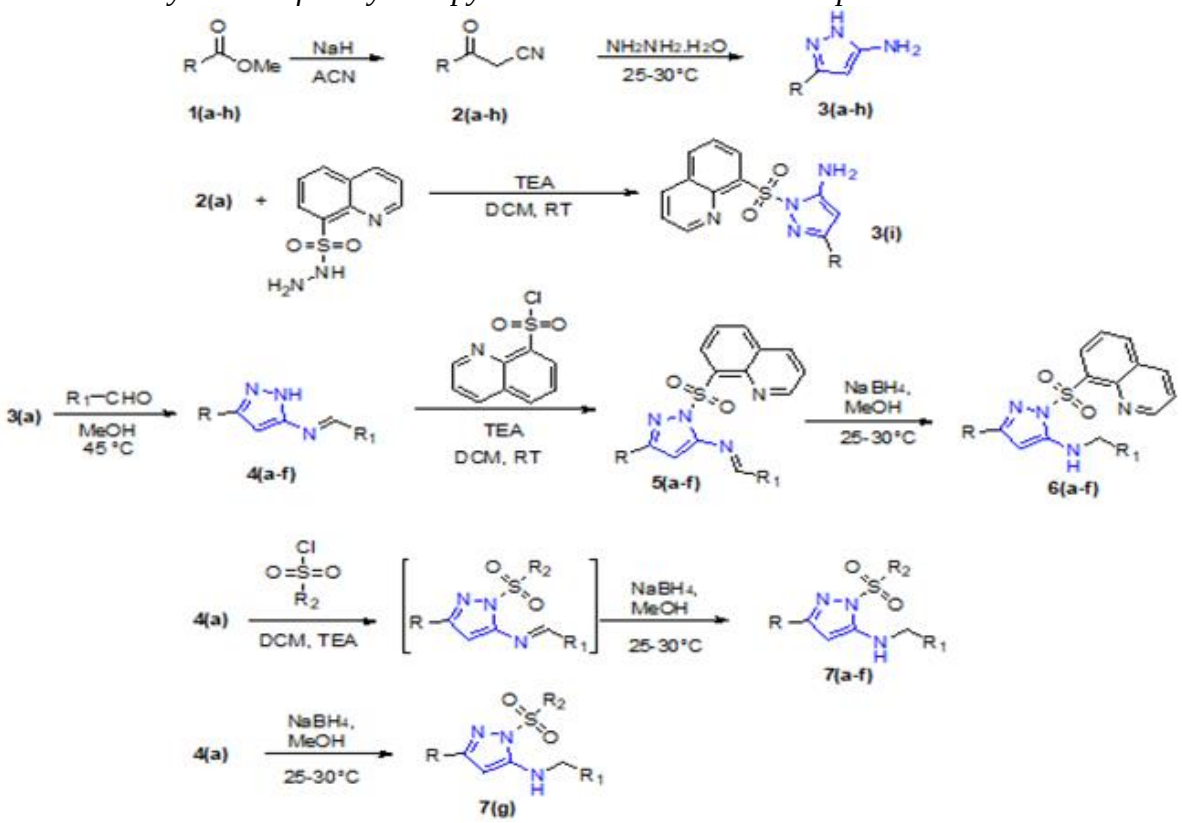
Keywords: 3-phenyl-1*H*-pyrazol-5-amine, 5-amino-1*H* –pyrazoles, Pyrazoles, Sulfonami

1. INTRODUCTION
5-Amino pyrazole is a 5 membered- heterocyclic system in which 2 nitrogen present adjacent to each other. Substituted 3-Phenyl-1*H*-Pyrazol-5-Amine and their derivatives exhibit high biological activities. Synthesis of 3-phenyl-1*H*-pyrazol-5-amines has been comprehensively investigated in the last few decades. Pyrazole and its derivatives are shown variable biological and pharmacological activities such as: anticancer[1,2], anti-inflammatory[3,4], antioxidant [5], antifungal [6], antibacterial [6,7,8], analgesic [9], antiviral [10,11], antimicrobial [12,13], antiglycemic[14], antiamoebic[15], and antidepressive [16,17]. Pyrazole is one of the most popular heterocycles in bioactive compounds, including drugs and agrochemicals [18, 19]. By considering these substantial biological applications of pyrazole, it is one of the most widely studied nitrogen-containing heterocyclic nuclei. Pyrazole derivatives are composed of the pyrazole nucleus attached to other heterocyclic or aromatic moieties which facilitate them to exhibit improved pharmacological activities. Several conventional methods are available for the synthesis of 3-aryl-1*H*-pyrazol-5-amines and its derivatives which has limitations like harsh reaction condition, longer reaction time, low yields. But yet microwave assisted synthesis of 3-aryl-1*H*-pyrazol-5-amines are neglected.
So considering of all these facts, in the present work we wish to synthesis of series of 3-phenyl-1*H*-pyrazol-5-amine under microwave irradiation and their derivatization into variety of imines, amines and sulfonamides.

2. RESULTS AND DISCUSSION

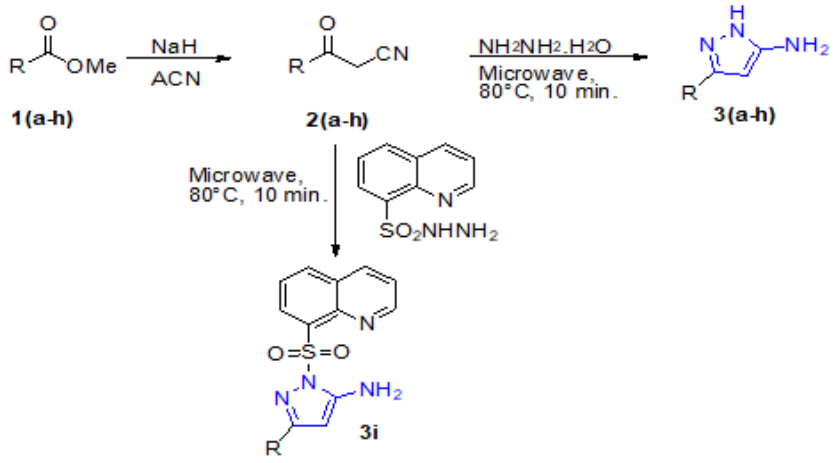
Reaction conditions of all steps were optimized with respect to stoichiometry of reagents, reaction temperature, Reaction time and reaction solvent. Optimized reaction condition was used during synthesis of all step intermediates.

Scheme-1: *Synthesis of 3-aryl-1H-pyrazol-5-amines and their explorations*



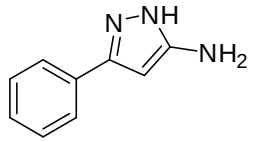
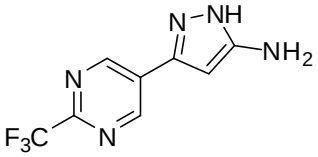
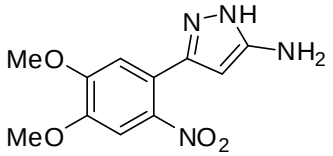
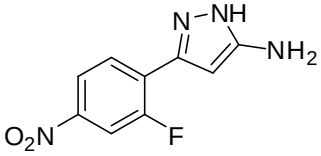
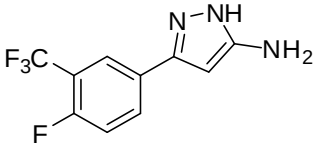
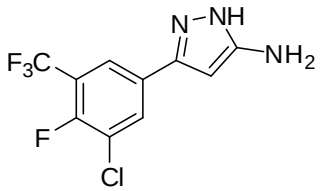
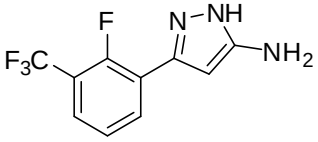
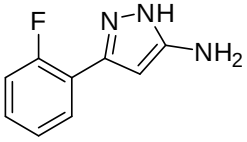
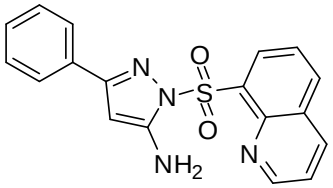
As an effort to synthesis of 3-aryl-1*H*-pyrazol-5-amines from benzoylacetonitrile under microwave irradiation and their exploration was described herein the present article. Several methods were reported for the synthesis of benzoylacetonitrile followed by cyclizations to get desired 3-aryl-1*H*-pyrazol-5-amine.

Scheme-2: *Synthesis of substituted 3-aryl-1H-pyrazol-5-amines 3(a-h) & 3i.*

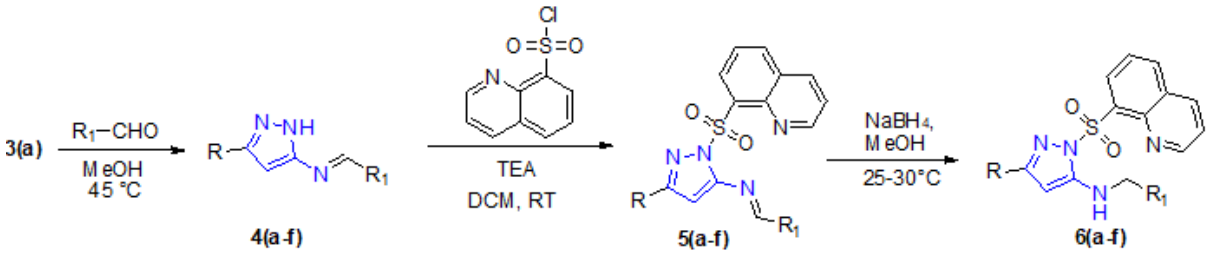


Elimination of methoxy group of methyl benzoate ***1(a-h)*** with acetonitrile (ACN) in presence of sodium hydride as a base in DMSO resulted in the formation of benzoylacetonitrile ***2(a-h)*** derivatives, respectively.[20] The compounds ***2(a-h)*** cyclocondensed with two equivalents of hydrazine hydrate under microwave irradiation for 10 min at 80°C in absence of solvent to afford 3-aryl-1*H*-pyrazol-5-amines ***3(a-h)*****(Scheme-2)**. The structure of compounds ***3(a-h)*** was confirmed by their physical properties (melting point) and ^{1}H-NMR spectral data. Details of synthesized substituted 3-aryl-1*H*-pyrazol-5-amines were summarized in **Table -1**.

Table-1: *Microwave assisted, solvent free Synthesis of substituted 3-aryl-1H-pyrazol-5-amines-3(a-h) &3i.*

 **3a, 95%**	 **3b, 83%**	 **3c 84%**
 **3d, 89%,**	 **3e, 85%,**	 **3f 81%,**
 **3g, 88%,**	 **3h, 93%,**	 **3i, 68%,**

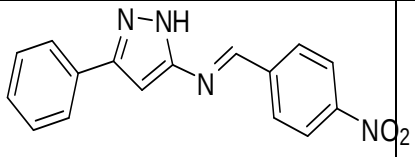
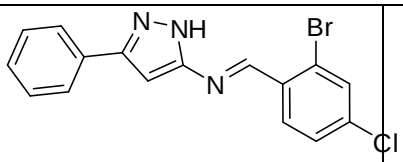
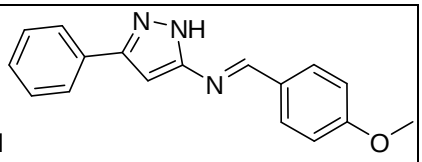
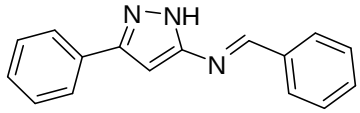
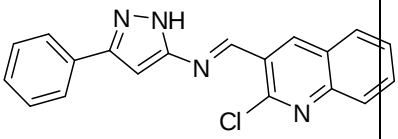
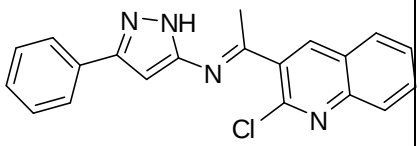
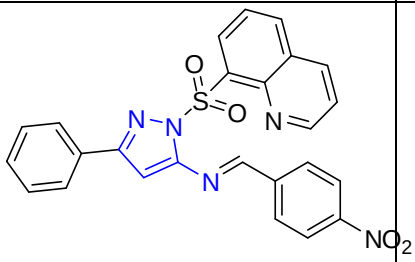
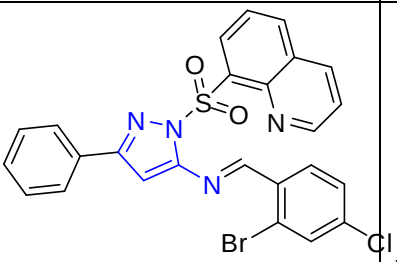
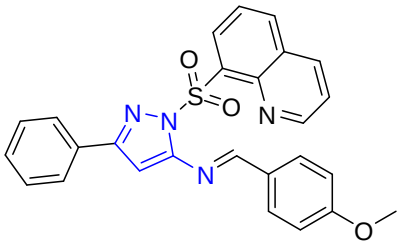
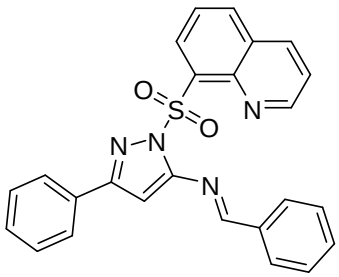
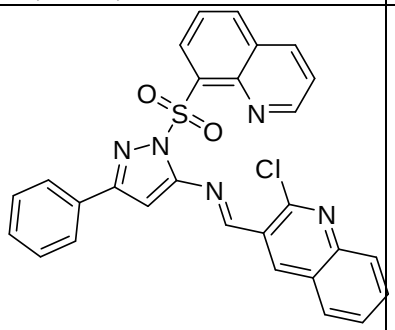
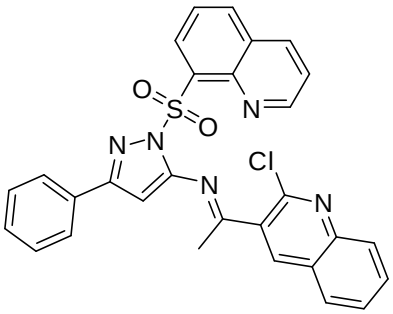
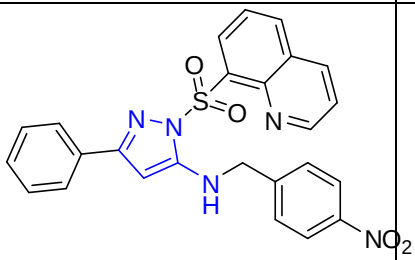
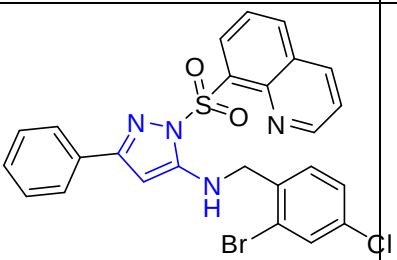
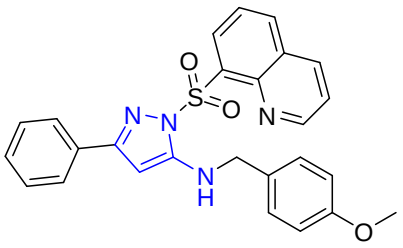
Scheme-3: *Exploration of 3-Phenyl-1H-pyrazol-5-amines 3(a) using substituted aromatic benzaldehydes.*

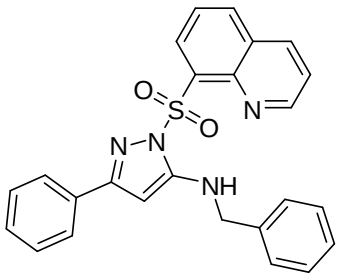
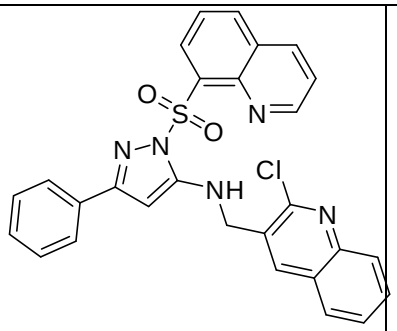
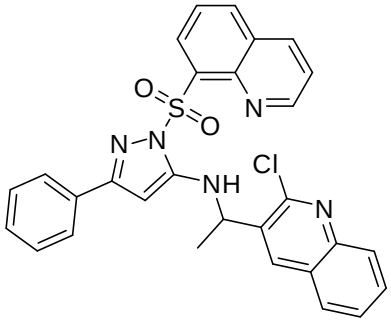


The 3-Phenyl-1*H*-pyrazol-5-amines ***3(a)*** was taken as key intermediates to synthesize substituted-(E)-N-benzylidene-3-phenyl-1*H*-pyrazol-5-amine ***4(a-f)*** and their derivatives, incorporated with 8-quinoline sulfonamide. Treatment of 3-Phenyl-1*H*-pyrazol-5-amines ***3(a)*** with substituted aromatic benzaldehydes was performed in polar protic solvent (Methanol) at ambient temperature, afforded the target substituted-(E)-N-benzylidene-3-phenyl-1*H*-pyrazol-5-amine ***4(a-f)*** intermediates. Thus compounds ***4(a-f)*** was treated at first with one equivalents of 8-quinoline sulfonyl chloride and triethylamine in dichloromethane at ambient temperature to prepare the corresponding substituted-(E)-N-benzylidene-3-phenyl-1-(quinolin-8-ylsulfonyl)-1H-pyrazol-5-amine ***5(a-f)*** which on treatment with 1.5 eq. Sodium borohydride in 10 volume Methanol at ambient temperature to obtain substituted- N-benzyl-3-phenyl-1-

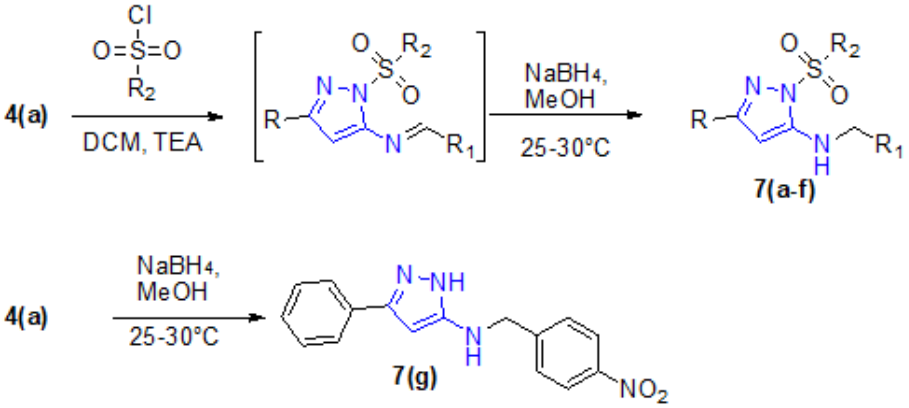
(quinolin-8-ylsulfonyl)-1*H*-pyrazol-5-amine ***6(a-f)*** as a isolable product. The structure of ***6(a-f)*** was confirmed by its spectral data (^{1}H-NMR). Details of synthesized compounds *[**4(a-f)**, **5(a-f)**, **6(a-f)**]* are summarized in **Table -2**.

Table-2: *Exploration of 3-Phenyl-1H-pyrazol-5-amines 3(a) using substituted aromatic benzaldehydes.*

 **4a, 96%,**	 **4b, 92%,**	 **4c, 94%,**
 **4d, 98%,**	 **4e, 78%,**	 **4f, 69%,**
 **5a, 65%,**	 **5b, 63%,**	 **5c, 69%,**
 **5d, 72%,**	 **5e, 59%,**	 **5f, 55%,**
 **6a,71%,**	 **6b, 66%,**	 **6c, 59%,**

 **6d, 75%**	 **6e, 58%**	 **6f, 55%**

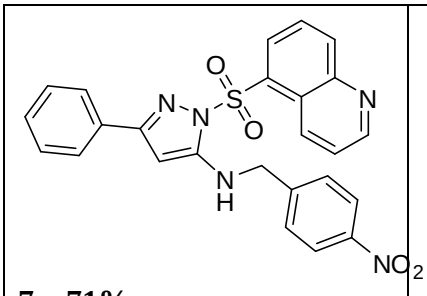
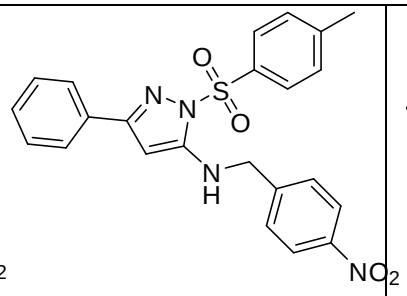
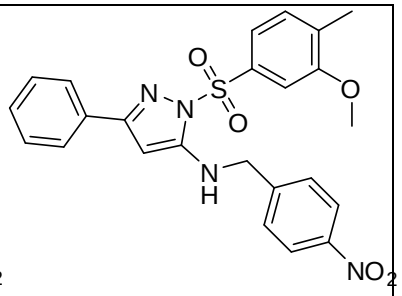
Scheme-4: *Exploration of 3-Phenyl-1H-pyrazol-5-amines 3(a) using substituted sulfonyl chlorides.*

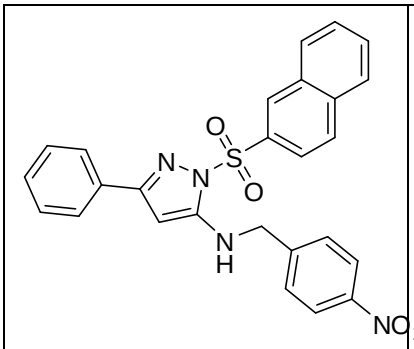


The (E)-N-(4-nitrobenzylidene)-3-phenyl-1*H*-pyrazol-5-amine ***4(a)*** was taken as key intermediates to synthesize sulfonamide derivatives ***7(a-f).***

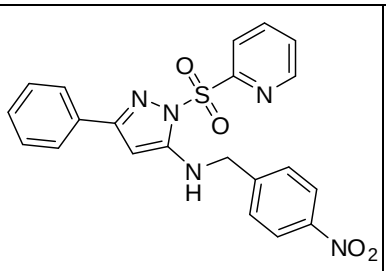
Treatment of (E)-N-(4-nitrobenzylidene)-3-phenyl-1*H*-pyrazol-5-amine ***4(a)*** with one equivalents of diversified sulfonyl chlorides and triethylamine in dichloromethane at ambient temperature to prepare the corresponding imine- sulfonamide derivatives which on treatment with 1.5 eq. sodium borohydride in 10 volume methanol at ambient temperature to obtain desired isolable target compounds ***7(a-f)***. The structure of ***7(a-f)*** was confirmed by its spectral data (*1H*-NMR). Details of synthesized compounds are summarized in **Table -3**.

Table-3: *Exploration of 3-Phenyl-1H-pyrazol-5-amines 3(a) using substituted sulfonyl chlorides.*

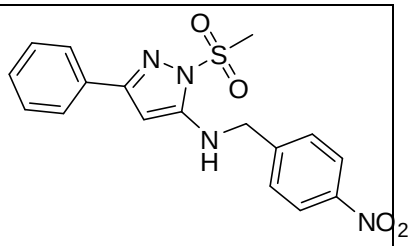
 **7a, 71%,**	 **7b, 58%,**	 **7c, 49%,**



7d, 49%,



7e, 56%,



7f, 63%,

3. EXPERIMENTAL SECTION

All chemicals and reagents were purchased from commercial resources like Avra, Spectrochem and Finar and utilized directly without purification. Reaction progress was monitored on TLC plate of silica-gel and visualized under UV light. Melting points were obtained by using Lab-India MR. Vis+ apparatus. The ^{1}H-NMR spectra were determined using Bruker 300 MHz instrument using TMS as the internal standard. Isolated compounds were purified using re-crystallization technique. All the synthesized products are reported in literature and were identified by comparison of their observed melting points and 1H-NMR values with reported values.

3.1 Preparation of Benzoylacetonitrile 2(a-h)

Sodium hydride (60%, 15.08 g, 377.0 mmol) in a round bottom flask was cooled using an ice-water bath and kept under nitrogen atmosphere on a schlenk line. Anhydrous acetonitrile (19.0 mL, 360 mmol) and 10.0 mL of anhydrous DMSO were added to the flask and the mixture was stirred for 20 minutes. Methyl benzoate (37.8 mL, 40.8 g, 300 mmol) was added to the reaction mixture. After stirring for approximately 1.5 hours, the reaction mixture turned into a thick white solid. The excess NaH in the reaction mixture was quenched by slow addition of deionized water. HCl (62.3 mL 12.1 M, diluted to 600 mL) was added to fully protonate the product, which immediately gave a milky white suspension. The product was then extracted three times (150 ml each) with ethyl acetate. All organic layers were combined and washed with NaCl brine. The organic layer was dried over anhydrous MgSO4 and filtered. Solvent was evaporated under reduced pressure, giving a light orange oil, which, when triturated with a 1:1 mixture of hexane and diethyl ether, yielded 41.33 g (284.7 mmol, 95%) of 1a as a very light yellow solid. All the synthesized products are reported in literature and were identified by comparison of their observed melting points and *1H*-NMR values with reported values.

3.2 Preparation of 3-aryl-1*H*-pyrazol-5-amines 3(a-h).

A mixture of benzoylacetonitrile **2(a)** (1.0eq.) and hydrazine hydrate (2.0eq.) was irradiated under microwave at 80°C for 10 min. Progress of the reaction was monitored by TLC. After completion of reaction, reaction mass diluted with cold water and filtered out under vacuum to get crude material which was washed with water. The crude product purified with recrystalisation using ethanol solvent to afford 3-aryl-1*H*-pyrazol-5-amines **3(a)** as a pale yellow solid with excellent yield. Synthesized compound characterized by their melting point and *1H*-NMR by comparing with reported values.

3a: 3-phenyl-1H-pyrazol-5-amine: *^{1}H-NMR (DMSO-d6, 300 MHz): d (ppm): 11.74 (Bs, 1H), 7.63-766 (d, 2H), 7.23-7.39 (m, 3H), 5.76 (s, 1H), 4.77 (s, 2H).*

Same protocol employed for the synthesis of remaining targets 3(b-f) and compounds are confirmed by comparing Melting point and *1H*-NMR with reported ones.

3.3 Preparation of 3-phenyl-1-(quinolin-8-ylsulfonyl)-1H-pyrazol-5-amine *3(i)*.

A mixture of benzoylacetonitrile *2(a)* (1.0eq.) and quinoline-8-sulfonohydrazide (1.0eq.) was irradiated under microwave at 80°C for 10 min in 10.0 rel. vol. ethanol. Progress of the reaction was monitored by TLC. After completion of reaction, reaction mass filtered out under vacuum to get crude material. The crude product purified with recrystalisation using hot ethanol to afford 3-phenyl-1*H*-pyrazol-5-amines **3(g)** as a pale yellow solid with good to excellent yield. Synthesized compound characterized by their melting point and *1H*-NMR by comparing with reported values.

3i:(3-phenyl-1-(quinolin-8-ylsulfonyl)-1*H*-pyrazol-5-amine): ^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 9.13 (dd, 2H), 8.40-8.45 (m, 2H), 8.12-8.16 (m, 1H), 7.94-7.99 (m, 1H), 7.72-7.81 (m, 2H), 7.35-7.51 (m, 3H), 6.53 (s, 2H), 6.31 (s, 1H).

3.4 Preparation of substituted-(E)-N-benzylidene-3-phenyl-1*H*-pyrazol-5-amine *4(a-f)*

3-Phenyl-*1H*-pyrazol-5-amines (3a) (1.0eq) stirred with 4-methoxy benzaldehyde (1.0eq.) in 3.0 rel volume methanol at 40-50°C for 5-6 h. Progress of the reaction monitotred by TLC. After completion of reaction, reaction mass cooled to 0-5°C. Precipitated solid product was filtered out under vacuum to afford (E)-N-(4-methoxybenzylidene)-3-phenyl-1*H*-pyrazol-5-amine ***4(c)*** as a solid with good yield. Synthesized compounds were characterized by *1H*-NMR.

4c: (E)-N-(4-methoxybenzylidene)-3-phenyl-1H-pyrazol-5-amine: ^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 8.76 (s, 1H), 7.89-7.91 (d, 2H), 7.75-7.78 (d, 2H), 7.28-7.48 (m, 3H), 6.99-7.02 (d, 2H), 6.62 (s, 1H), 3.90 (s, 3H), 3.50(3H).

Same protocol employed for the synthesis of remaining targets 3(b-f) and compounds are confirmed by comparing Melting point and *1H*-NMR with reported ones.

3.5 Preparation of substituted-(E)-N-benzylidene-3-phenyl-1-(quinolin-8-ylsulfonyl)-1H-pyrazol-5-amine 5(a-f).

(E)-N-(4-methoxybenzylidene)-3-phenyl-1*H*-pyrazol-5-amine (4c) (1.0eq) and 8-quinoline sulfonyl chloride (1.0eq) refluxed with triethylamine (2.0eq.) in 10.0 rel volume dichloromethane at reflux temperature for 8-10 h. Progress of the reaction monitotred by TLC. After completion of reaction, reaction mass was filter out under vacuum. Filtrate mL concentrated to obtain crude product. This crude product was purified with ethanol crystallization to afford (E)-N-(4-methoxybenzylidene)-3-phenyl-1-(quinolin-8-ylsulfonyl)-1*H*-pyrazol-5-amine **5(c)** as a white solid with moderate yield. Synthesized compounds were characterized by *1H*-NMR.

5b:(E)-N-(2-bromo-4-chlorobenzylidene)-3-phenyl-1-(quinolin-8-ylsulfonyl)-1H-pyrazol-5-amine: ^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 9.38-9.40 (dd,2H), 9.35 (s,1H), 9.10-9.32 (d, 2H), 8.44-8.47 (d, 2H), 7.98-8.21 (d, 2H), 7.22-7.94 (m, 6H), 7.00 (s, 1H).

5c:(E)-N-(4-methoxybenzylidene)-3-phenyl-1-(quinolin-8-ylsulfonyl)-1H-pyrazol-5-amine: ^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 9.31 (dd, 2H), 8.85 (s, 1H), 8.43-8.47 (dd, 2H), 8.16-8.18 (d, 1H), 7.97-8.02 (d, 1H), 7.88-7.91 (d, 2H), 7.78-7.81 (d, 2H), 7.32-7.48 (dd, 3H), 7.08-7.11(d,2H), 6.85(s1H), 3.85(s, 3H).

Same protocol employed for the synthesis of remaining targets 3(b-f) and compounds are confirmed by comparing Melting point and 1*H*-NMR with reported ones.

3.6 Preparation of substituted-N-benzyl-3-phenyl-1-(quinolin-8-ylsulfonyl)-1H-pyrazol-5-amine 6(a-f)

(E)-N-(4-nitrobenzylidene)-3-phenyl-1-(quinolin-8-ylsulfonyl)-1*H*-pyrazol-5-amine **(5a)** (1.0eq) and sodium borohydride (1.5eq) stirred in 10.0 volume methanol at 25-30°C for 8-10 h. Progress of the reaction monitotred by TLC. After completion of reaction, reaction mass concentrated under vacuum to get thick solid. Isolated solid diluted with water, *pH* adjusted 5-6 by 6N HCl and extracted with dichloromethane. Dichloromethane on concentration provided

crude product which was purified with column chromatography to afford N-(4-nitrobenzyl)-3-phenyl-1-(quinolin-8-ylsulfonyl)-1*H*-pyrazol-5-amine 6(a) a solid with moderate yield. Synthesized compounds were characterized by 1*H*-NMR.

6a: N-(4-nitrobenzyl)-3-phenyl-1-(quinolin-8-ylsulfonyl)-1H-pyrazol-5-amine:^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 8.23-8.26 (d, 2H), 7.79-7.81 (d, 2H), 7.64-7.67 (d, 2H), 7.46-7.52 (m, 7H), 7.11-7.13 (d, 2H), 6.31 (t, 1H), 4.58 (d, 2H).

6b:N-(2-bromo-4-chlorobenzyl)-3-phenyl-1-(quinolin-8-ylsulfonyl)-1H-pyrazol-5-amine:-^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 9.13 (s,2H), 8.15-8.18 (d, 2H), 8.11-8.14 (d, 1H), 7.80-7.93 (m, 5H), 7.60-7.62 (d, 2H), 7.31-7.50 (m, 5H), 6.97 (s, 1H), 4.64 (d, 2H).

Same protocol employed for the synthesis of remaining targets 3(b-f) and compounds are confirmed by comparing Melting point and 1*H*-NMR with reported ones.

3.7 Preparation of 7(a-f)

(E)-N-(4-nitrobenzylidene)-3-phenyl-1*H*-pyrazol-5-amine (1.0eq) and p-Toluene-sulfonyl chloride (1.0eq) refluxed with triethylamine (2.0eq.) in 10.0 rel volume dichloromethane at reflux for 8-10 h. Progress of the reaction monitotred by TLC. After completion of reaction, reaction mass was filtered out under vacuum. Filtrate mL concentrated to obtain crude product which was diluted with methanol (3.0 rel vol) and treated with 1.5 eq. sodium borohydride. Progress of the reaction monitored by TLC. After completion of reaction, reaction mass concentrated under vacuum to get thick solid. Isolated solid diluted with water, *pH* adjusted 5-6 by 6N-HCl and extracted with dichloromethane. Dichloromethane on concentration provided crude product which was purified with column chromatography to afford (E)-N-(4-nitrobenzylidene)-3-phenyl-1-tosyl-1*H*-pyrazol-5-amine ***7(b)*** a solid with low to moderate yield. Synthesized compounds were characterized by 1*H*-NMR.

7b: N-(4-nitrobenzyl)-3-phenyl-1-tosyl-1*H*-pyrazol-5-amine:^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 9.27-9.38 (dd, 2H), 8.41-8.46 (d, 2H), 8.13-8.21 (d, 3H), 7.96-8.01 (m, 1H), 7.63-7.66 (m, 3H), 7.29-7.42 (m, 3H), 5.91 (t, 1H), 4.64 (d, 2H), 2.10 (s, 3H).

7c: Ethyl 4-(2,4-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate: ^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 8.14 (dd, 4H), 7.64-7.99 (m, 6H), 7.51-7.55 (m, 3H), 6.33 (t, 1H), 4.59 (d, 2H), 3.90 (s, 3H), 2.22 (s, 3H).

Same protocol employed for the synthesis of remaining targets 3(b-f) and compounds are confirmed by comparing Melting point and *1H*-NMR with reported ones.

3.8 Preparation of N-(4-nitrobenzyl)-3-phenyl-1*H*-pyrazol-5-amine 7(g):

(E)-N-(4-nitrobenzylidene)-3-phenyl-1*H*-pyrazol-5-amine (1.0eq) and sodium borohydride (1.5eq) stirred in 10.0 rel vol. methanol at 25-30°C for 8-10 h. Progress of the reaction monitotred by TLC. After completion of reaction, reaction mass filtered out under vacuum to provide crude product which was purified with column chromatography to afford N-(4-nitrobenzyl)-3-phenyl-1*H*-pyrazol-5-amine **7(g)** as a white solid with 97.0% yield, ^{1}H-NMR (DMSO-d6, 300 MHz): d (ppm): 8.21-8.24 (d, 2H), 7.59-762 (d, 2H), 7.37-7.52 (m, 6H), 5.87 (s, 1H), 4.56-4.58 (d, 2H).

4. CONCLUSION

An efficient, mild, and green methodology has been developed for the synthesis of 3-aryl-1*H*-pyrazol-5-amines under microwave irradiation using benzoylacetonitrile and hydrazine hydrate in absence of solvent. The developed methodology has a simple isolation process with good to excellent yields; relatively short reaction times are some advantages of this protocol. This improved reaction condition allows the preparation of a wide variety of substituted 3-aryl-1*H*-pyrazol-5-amines in high to good yields and excellent purity under mild reaction conditions. We believe the applicability of this methodology with the mentioned advantages makes our

method superior among other reported methods to synthesize substituted 3-aryl-1*H*-pyrazol-5-amines.

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