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Efficient and novel one-pot synthesis of antifungal active 1-substituted-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines using solid support

Monika Gupta*, Satya Paul, Rajive Gupta

Department of Chemistry, University of Jammu, Jammu-180006, India

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ABSTRACT

A simple, efficient and environment-friendly procedure is developed for the synthesis of 1-substitued-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines in the presence of *N*,*N*-dimethylformamide as an energy transfer medium, *p*-TsOH as catalyst and basic alumina as solid support under microwave irradiation. The products are obtained in moderate to good yields and are in a state of high purity. Moreover, title compounds have been screened for antifungal activity.

1. Introduction

Heterocyclic compounds, whether natural or synthetic show interesting biological activities and are often key components in various biological processes. Nitrogen containing heterocycles have attracted considerable attention due to their wide range of pharmacological activities. For instance, a number triazole derivatives are known to possess antifungal [1,2], antibacterial [3], antiinflammatory [4], antimicrobial [5,6], tuberculo-therapeutic [7] and antiasthmatic [8] activities. Benzotriazepine derivatives [9], were also reported to possess antibacterial, antiviral and psychotropic activities [10,11]. Some of these derivatives were used in the manufacture of plant protecting agents [12]. The malaria therapy, acaricidal, herbicidal and insecticidal properties [13] of benzotriazepine analogues have also been documented. A variety of pyrazole derivatives are associated with wide range of biological activities [14] such as antifungal, antibacterial activities etc. by virtue of incorporating toxophoric C=N linkage. In order to study the additive effect of three heterocyclic moieties in a single frame work, there is a continued interest in the synthesis of 1-substituted-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo [4,3-*b*][1,2,4]triazepines (**3a**–**j**). This paper reports an efficient and novel one-pot synthesis of 1-substituted-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines by irradiating a mixture of 5-aryl-3,4-diamino-1,2,4-triazoles and (1-substituted -3-alkyl/aryl-5-chloropyrazol-4-yl)formaldehydes in the presence of *N*,*N*-dimethylformamide as an energy transfer medium, *p*-TsOH as catalyst and basic alumina as solid support under microwave irradiation as well as stirring in an oil-bath at 80 °C.

2. Results and discussion

In our earlier communication, we reported the synthesis of 1-suibstitued-3,7-dialkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines [15]. Here, we report the modification of our previously reported tricyclic heterocyclic core pyrazolo triazolotriazepines to generate 1-substituted-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines as potential antifungal agents. The required precursor, 5-aryl-3,4-diamino-1,2,4-triazoles (**1**) and (1-substituted-3-alkyl/aryl-5-chloropyrazol-4-yl)formaldehydes (**2**) were condensed to afford title compounds (**3a**–**j**) in *N*,*N*-dimethylformamide as an energy transfer medium, *p*-TsOH as catalyst and basic alumina as solid support under microwave irradiation (Scheme 1). Physical data of these compounds is summarized in Table 1.

In order to optimize the reaction conditions, (3-methyl-5-chloropyrazol-4-yl)formaldehyde (**2a**) and 5-phenyl-3,4-diamino-

* Corresponding author.
E-mail address: monika.gupta77@indiatimes.com (M. Gupta).

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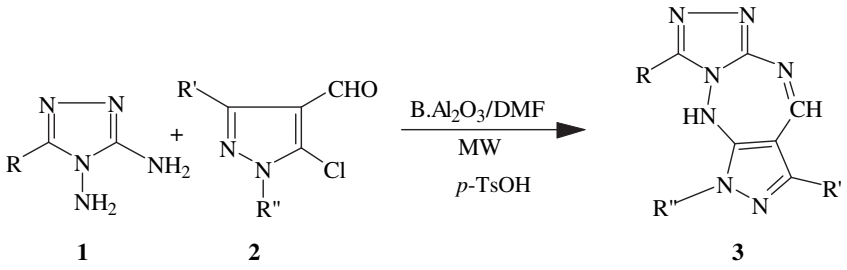

Scheme 1. Synthesis of 1-Substituted-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines using basic alumina, *p*-TsOH and *N*,*N*-dimethylformamide under microwave irradiation (Power = 640 W). **3a**: R = C_6H_5, R′ = CH_3, R″ = H. **3b**: R = 4-ClC_6H_4, R′ = CH_3, R″ = H. **3c**: R = C_6H_5, R′ = C_6H_5, R″ = C_6H_5. **3d**: R = $CH_2C_6H_5$, R′ = 4-BrC_6H_4, R″ = C_6H_5. **3e**: R = 4-ClC_6H_4, R′ = 4-BrC_6H_4, R″ = C_6H_5. **3f**: R = (4-NO_2)C_6H_4, R′ = 4-BrC_6H_4, R″ = C_6H_5. **3g**: R = C_6H_5, R′ = 4-BrC_6H_4, R″ = C_6H_5. **3h**: R = C_6H_5, R′ = (4-NO_2)C_6H_4, R″ = C_6H_5. **3i**: R = $CH_2C_6H_5$, R′ = (4-NO_2)C_6H_4, R″ = C_6H_5. **3j**:R = (4-NO_2)C_6H_4, R′ = (4-NO_2)C_6H_4, R″ = C_6H_5.

1,2,4-triazole (**1a**) were selected as test substrates in an open vessel. It was found that for 5 mmol of each of 5-phenyl-3,4-diamino-1,2,4-triazole (**1a**), (3-methyl-5-chloropyrazol-4-yl)formaldehyde (**2a**), 2.5 mmol of *N*,*N*-dimethylformamide, 200 mg of *p*-TsOH and basic alumina was required to get maximum yield under mild reaction conditions. The test reaction was carried out at different power levels from 80 to 900 W and it was found that 640 W was the optimum power level as far as yield and reaction times are concerned.

In order to determine the possibility of a specific microwave effect accelerating the reaction with respect to conventional heating, a pre-heated oil-bath was used as a source of heat in comparative experiments. The lower yields were obtained with conventional heating under the same conditions of time, indicate that the effect of microwave is not purely thermal. The reaction is faster in the microwave experiment than under conventional heating at the same time and same temperature because this is the characteristic feature of microwave irradiations that reactions with polar substrates carry out at a fast rate. Moreover, the heating starts from interior than exterior as in case of conventional heating.

To sum up, the microwave irradiation provides an excellent methodology for the synthesis of 1-substituted-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines to be performed in 4–25 min.

The important findings while carrying out the reaction was that the heterocyclic core pyrazolo triazolotriazepine was composed of three heterocyclic moieties and each were associated with broad spectrum of activities while in condensed system, the title compounds were known for antifungal activity. Moreover, reactions were fast and yields were more as compared to conventional heating. The reason was that these contained polar groups that made the molecule polar and the polar molecules were microwave active. Also, the reaction was carried out in high boiling point polar solvent i.e. high dielectric constant that made the reaction highly microwave active. This is what the reaction yields were more under microwave irradiation.

Table 1
Physical data of synthesized compounds 1-Substituted-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines using basic alumina, *p*-TsOH and *N*,*N*-dimethylformamide under microwave irradiation (Power = 640 W).

Product[a]	Time[b] (min)
3a[c]	11
3b[c]	4
3c[c]	20
3d[d]	23
3e[c]	17
3f[d]	14
3g[c]	25
3h[c]	8
3i[c]	13
3j[c]	22

[a] Products were characterized by ^{1}H NMR, IR and mass spectral data.
[b] Time was measured by immersing the glass thermometer in reaction mixture by giving a short pulse of 5 s followed by 5 s cooling time.
[c] Products were purified by crystallization from ethyl acetate.
[d] Products were purified by passing through a column of alumina and elution with ethyl acetate and petroleum ether in the ration of (2:8).

3. Antifungal activity

Fungal infections have been reported to have dramatically increased in the past decade, and these often occur as systemic infections or as coinfections with other diseases, such as AIDS or cancer, or in patients who are immunocompromised. In fact, candidiasis has become the most common infection in AIDS and cancer patients. Unfortunately, in addition to the limited number of antifungal drugs currently available, fungal infections tend to rapidly develop resistance to these drugs. For these reasons, fungal infections now show much higher mortality rates than bacterial infections.

The rapid increase in fungal infections and the growing number of new antifungal agents indicate an increasing need for rapid and accurate methods for antifungal screening and susceptibility testing. The National Committee for Clinical Laboratory Standards (NCCLS) recently approved a standardized method for antifungal susceptibility testing, and proposed a method for testing of filamentous fungi, based on a broth macrodilution method (BMM). Subsequently, several modifications of these methods were proposed. Most of these methods were developed for the determination of MICs of agents against yeasts.

Heterocyclic compounds exhibit a broad spectrum of biological activities. Keeping in view the biological importance of condensed heterocyclic compounds, the title compounds were evaluated for the antifungal activity against *Aspergillus flavus*, *Aspergillus niger*, *Rhizopus species* and *Penicillium species* by paper disc technique against the concentration 500 μg and 1000 μg. The zone of inhibition after 24 h of incubation at 28 ± 2 °C was compared with that of standard fluconazole. The screening data indicated that the compounds **3a**, **3b**, **3c**, **3e**, **3h** and **3j** showed moderate activity against *Penicillium species* and *Rhizopus species*, while low activity was observed against *A. niger* and *A. flavus*. Some of the synthesized compounds were screened for antifungal activity against *A.*

flavus, *A. niger*, *Rhizopus species* and *Penicillium species* by paper disc technique against two concentrations 500 μg/mL and 1000 μg/mL. The zone of inhibition after 24 h of incubation at 28 ± 2 °C was compared with that of identical concentrations of standard fluconazole. The screening data indicated that the compounds **3d**, **3f**, **3g** and **3i** showed excellent activity against *A. niger* and *Penicillium species* at 500 μg as well as 1000 μg concentrations whereas, these compounds showed good to moderate activity against *A. flavus* and *Rhizopus species* at both the concentrations as shown in Table 2.

The medium used for evaluation of antifungal activity was Potato dextrose agar -agar medium.

3.1. Experimental

3.1.1. Preparation of the medium

Potato dextrose agar -agar medium [16] was prepared as below:

Potato = 250 g; Dextrose = 10 g; Agar-agar = 20 g; Distilled water = 100 mL

Sliced potatoes were taken with 500 mL of distilled water in a pan and boiled for half an hour till a spoon when placed on a slice can pierce into it. Filter it while in hot and broth was again taken in a pan with rest of the distilled water. Dextrose dissolved in distilled water and weighed agar-agar was added to the broth and heated it to boil. The medium thus obtained was sterillized in pressure cooker for 30 min and few drops of streptomycin were added to prevent it from any bacterial contamination. The zone of inhibition was measured after 24 h, fluconazole (500 μg/mL and 1000 μg/mL) was used as control standard.

3.2. Procedure

Potato dextrose medium was prepared and sterilized in pressure cooker for 30 min. Sterillized medium (15 mL) each was pipetted out into flat petridishes. When it solidified 15 mL of warm seeded medium was applied over it. The seeded agar was made by cooling the medium to 40 °C and then adding spore suspension to seeded medium. The spores were obtained from ten days culture of *A. niger*, *A. flavus*, *Penicillium species* and *Rhizopus species*. Before the solidification of agar, the plate was tilted to ensure that coverage should be even. These petridishes were then put into the refrigerator upside down to prevent condensation of moisture. Two concentrations *viz*. 500 and 1000 μg/mL of the synthesized compounds were prepared by dissolving the required quantity of compounds in DMF. Sterilized Whatman filter paper number 541 discs were prepared by cutting 6 mm diameter with a cork borer and were spread individually with a needle and planted upon the chilled seeded medium. The plates were then incubated for 24–72 h at 28 °C±2 °C and inhibition of zone around each disc was measured from the centre of the discs. The percentage zone of inhibition was calculated by the formula

$$I\% = C - T/C \times 100$$

Where, I = inhibition

C = diameter of zone of micro- organisms in check

T = diameter of the disc

The zone of inhibition was measured after 24 h, fluconazole (500 μg/mL and 1000 μg/mL) was used as control standard.

4. Experimental

General. Melting points were determined on a Tempo melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DPX-200 NMR spectrometer (200 MHz) in $CDCl_3$ + DMSO-d_6 using tetramethylsilane as an internal standard and IR spectra were recorded using KBr disc on a Perkin Elmer FTIR spectrometer. The mass spectral data was obtained on a JEOL JMS-D 300 spectrometer. C, H, N and S were studied by Leco Analyzer (932). The reactions were carried out in domestic microwave oven LG Smart Chef MS-255R with maximum output power of 900 W having voltage 240 V to 50 Hz. Final temperature is measured by immersing glass thermometer in reaction mixture at the end of exposure to microwave irradiation and its approximate temperature range.

Table 2
Antifungal activity of title compounds 1-substituted-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines under microwave irradiation at 640 W.

S.No.	Product No.	Zone of inhibition in mm (%)							
		Aspergillus niger		Aspergilus Flavus		Rhizopus species		Pencillium species	
		500 μg	1000 μg	500 μg	1000 μg	500 μg	1000 μg	500 μg	1000 μg
1	**3a**	22 (36.66)	32 (53.33)	20 (33.33)	24 (40.00)	32 (53.33)	40 (60.66)	06 (10.00)	08 (13.33)
2	**3b**	23 (38.33)	32 (53.33)	22 (36.66)	24 (40.00)	31 (51.66)	40 (60.66)	08 (13.33)	09 (15.00)
3	**3c**	20 (33.33)	31 (51.66)	21 (35.36)	21 (35.36)	36 (66.66)	39 (65.00)	05 (8.33)	02 (3.33)
4	**3d**	02 (3.33)	14 (23.33)	20 (33.33)	08 (13.33)	28 (46.66)	24 (40.00)	05 (8.33)	–
5	**3e**	32 (53.33)	21 (35.36)	22 (36.66)	24 (40.00)	40 (60.66)	32 (53.33)	09 (15.00)	08 (13.33)
6	**3f**	14 (23.33)	02 (3.33)	18 (31. 33)	08 (13.33)	24 (40.00)	21 (35.36)	02 (3.33)	05 (8.33)
7	**3g**	02 (3.33)	12 (21.33)	18 (31.33)	06 (11.33)	26 (42.66)	22 (38.00)	05 (8.33)	08 (13.33)
8	**3h**	31 (51.66)	20 (33.33)	24 (40.00)	22 (36.66)	39 (65.00)	36 (66.66)	07 (12.98)	09 (15.00)
9	**3i**	02 (3.33)	14 (23.33)	20 (33.33)	08 (13.33)	28 (46.66)	24 (40.00)	–	–
10	**3j**	08 (13.33)	15 (25.00)	03 (5.00)	09 (15.00)	18 (30.00)	23 (38.33)	–	–
11	Standard Fluconazole	42 (70.00)	48 (80.00)	35 (58.33)	42 (70.00)	38 (63.33)	42 (70.00)	52 (86.66)	54 (90.00)

5. General procedure for the synthesis of novel antifungal active 1-substituted-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines (3a–j)

A mixture of 5-aryl-3,4-diamino-1,2,4-triazole **1** (5 mmol), (1-substituted-3-alkyl/aryl-5-chloropyrazol-4-yl)formaldehyde **2** (5 mmol), *N*,*N*-dimethylformamide (2.5 mmol), *p*-TsOH (200 mg) and basic alumina (1 g) was mixed thoroughly in a borosil beaker (50 mL) with the help of a glass rod. The mixture was exposed to microwave irradiation for the appropriate time (monitored by TLC, shown in Table 1) at 640 W. After the completion of reaction, the mixture was extracted with hot *N*,*N*-dimethylformamide (3 × 15 mL). The solid obtained after pouring of the *N*,*N*-dimethylformamide extract onto the crushed ice, was collected, washed with water and dried. The crude product was purified either by crystallization from ethyl acetate or passing through a column of alumina and elution with ethyl acetate and petroleum ether (2:8). The physical data of the synthesized compounds is given in Table 1. The structures of the synthesized products were confirmed by ^{1}H NMR and mass spectral data.

6. Spectral data of the synthesized compounds (3a–j)

6.1. 8-Phenyl-3-methyl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepines (**3a**)

Light brown coloured solid, Yield (62%), M.p. 204–206 °C ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 2.28 (s, 3H, CH_3), 7.20–7.23 (m, 3H, H_{arom}), 7.45–7.50 (m, 2H, H_{arom}), 7.68 (s, 1H, C-4H), 8.15 (bs, 1H, NH); ^{13}C NMR: δ 158 (C-3, 7, 5a and 10a), 130 (C-4′), 129 (C-1′), 128 (C-3′, 5′), 127 (C-2′, 6′), 77 (C-3a), 41 (CH_2), 28(CH_3); (IR ν_{max} in cm^{-1}, KBr): 3600, 3026, 2854, 1625. *Anal. Calcd*. for $C_{13}H_{11}N_7$: C, 58.86; H, 4.15; N, 36.98. Found: C, 58.82; H, 4.12; N, 36.95. *m*/*z* (%) = 265 (M^+)

6.2. 8-(4′-Chlorophenyl)-3-methyl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepines (**3b**)

Pale yellow coloured solid, Yield (72%), M.p. 214–216 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 2.35 (s, 3H, CH_3), 7.30–7.37 (m, 2H, H_{arom}), 7.40–7.55 (m, 2H, H_{arom}), 7.70 (s, 1H, C-4H), 8.16 (bs, 1H, NH), 8.50 (bs, 1H, NH); ^{13}C NMR: δ 158 (C-3, 7, 5a and 10a), 136 (C-4″), 130 (C-4′, 1″), 129 (C-1′, 3″, 5″), 128 (C-3′, 5′, 2″, 6″), 127 (C-2′, 6′), 77 (C-3a), 41 (CH_2), 28(CH_3); IR (ν_{max} in cm^{-1}, KBr): 3100, 3020, 2800, 1622, 1415, 728. *Anal. Calcd*. for $C_{13}H_{10}N_7Cl$: C, 52.08; H, 3.33; N, 32.72; Cl, 11.85. Found: C, 52.04; H, 3.30; N, 32.70; Cl, 11.83. *m*/*z*(%) = 295.5(M^+).

6.3. N-Phenyl-3,8-diphenyl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine (**3c**)

Pale yellow coloured solid, Yield (68%), M.p. 192–194 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 7.08–7.23 (m, 2H, H_{arom}), 7.30–7.38 (m, 7H, H_{arom}), 7.5–7.52 (m, 6H, H_{arom}), 7.67 (s, 1H, C-4H), 8.54 (bs, 1H, NH); ^{13}C NMR: δ 158 (C-3, 7, 5a and 10a), 130 (C-4′, 4″, 4‴), 129 (C-1′, 1″, 1⁗), 128 (C-3′,3″,3⁗ 5″, 5‴, 5′), 127 (C-2′, 6′, 2″, 2‴, 6″, 6‴), 77 (C-3a), 41 (CH_2), 28(CH_3); IR (ν_{max} in cm^{-1}, KBr): 3060, 3010, 2800, 1602, 1415. *Anal. Calcd*. for $C_{24}H_{17}N_7$: C, 71.46; H, 4.21; N, 24.31. Found: C, 71.44; H, 4.20: N, 24.30. *m*/*z*(%) = 403 (M^+)

6.4. N-Phenyl-8-benzyl-3-(4″-bromophenyl)-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine (**3d**)

Yellow coloured solid, Yield (74%), M.p. 146–148 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 4.00 (s, 2H, Ar-CH_2), 7.20–7.28 (m, 6H, H_{arom}), 7.38–7.55 (m, 8H, H_{arom}), 7.69 (s, 1H, C-4H), 8.51 (bs, 1H, NH); ^{13}C NMR: δ 158 (C-3, 7, 5a and 10a), 135(C-4″), 130 (C-4′, 4‴), 129 (C-1′, 1″, 1⁗), 128 (C-3′,3″,3⁗ 5″, 5‴, 5′), 127 (C-2′, 6′, 2″, 2‴, 6″, 6‴), 77 (C-3a), 41 (CH_2), 28(CH_3); IR (ν_{max} in cm^{-1}, KBr): 3112, 3010, 1622, 1429, 562. *Anal. Calcd*. for $C_{25}H_{18}N_7Br$: C, 61.00; H, 3.66; N, 19.14; Br, 14.25. Found; C, 60.99; H, 3.64; N, 19.12; Br, 14.24. *m*/*z*(%) = 491(M^+)

6.5. N-(4‴Bromophenyl)-8-(4′-chlorophenyl)-3-phenyl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine (**3e**)

Brown coloured solid, Yield (64%), M.p. 210–212 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 7.23–7.45 (m, 9H, H_{arom}), 7.50–7.58 (m, 4H, H_{arom}), 7.70 (s, 1H, C-4H), 8.53 (bs, 1H, NH); ^{13}C NMR: δ 158 (C-3, 7, 5a and 10a), 142 (C-4‴), 137(C-4″), 130 (C-4′), 129 (C-1′, 1″, 1⁗), 128 (C-3′,3″,3⁗ 5″, 5‴, 5′), 127 (C-2′, 6′, 2″, 2‴, 6″, 6‴), 77 (C-3a), 41 (CH_2), 28(CH_3); IR (ν_{max} in cm^{-1}, KBr): 3110, 3030, 1404, 742, 592. *Anal. Calcd*. for $C_{24}H_{15}ClBrN_7$: C, 56.30; H, 2.97; Cl, 7.05; Br, 15.69; N, 19.46. Found: C, 56.25; H, 2.95; Cl, 7.04; Br, 15.69; N, 19.42. *m*/*z* (%) = 511.5 (M^+)

6.6. N-(4‴-Bromophenyl)-8-(4′-nitrophenyl)-3-phenyl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine (**3f**)

Brown coloured solid, Yield (68%), M.p. 178–180 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 2.32 (s, 3H, CH_3), 7.22–7.32 (m, 2H, H_{arom}), 7.38–7.52 (m, 2H, H_{arom}), 7.68 (s, 1H buried C-4H), 8.20 (bs, 1H, NH), 8.55 (bs, 1H, NH); ^{13}C NMR: δ 158 (C-3, 7, 5a and 10a),134 (C-4‴), 142 (C-4⁗), 137(C-4″), 130 (C-4′), 129 (C-1′, 1″, 1⁗), 128 (C-3′,3″,3⁗ 5″, 5‴, 5′), 127 (C-2′, 6′, 2″, 2‴, 6″, 6‴), 77 (C-3a), 41 (CH_2), 28(CH_3); IR (ν_{max} in cm^{-1}, KBr): 3110, 3040, 2810, 1612, 1410, 718. *Anal. Calcd*. for $C_{24}H_{15}N_8O_2Br$: C,55.17; H, 2.87; N,21.45; O, 6.13. Found: C, 55.15; H, 2.84; N, 21.42; O, 6.11. *m*/*z*(%) = 522 (M^+)

6.7. N-(4‴-Bromophenyl)-3,8-diphenyl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine (**3g**)

Yellow coloured solid, Yield (71%), M.p.168–170 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 7.12–7.32 (m, 7H, H_{arom}), 7.35–7.45 (m,7H, H_{arom}), 7.68 (s, 1H, C-4H), 8.55 (bs, 1H, NH); ^{13}C NMR: δ 158 (C-3, 7, 5a and 10a),134 (C-4‴), 142 (C-4⁗), 137(C-4″), 130 (C-4′), 129 (C-1′, 1″, 1⁗), 128 (C-3′,3″,3⁗ 5″, 5‴, 5′), 127 (C-2′, 6′, 2″, 2‴, 6″, 6‴), 77 (C-3a), 41 (CH_2), 28(CH_3); IR (ν_{max} in cm^{-1}, KBr): 3080, 3004, 1615, 1410, 556. *Anal. Calcd*. for $C_{24}H_{16}N_7Br$: C, 60.37; H, 3.35; N, 19.70; Br, 16.56. Found: C, 60.35; H, 3.32; N, 19.68; Br, 16.52. *m*/*z*(%) = 477 (M^+).

6.8. N-(4‴-Nitrophenyl)-3,8-diphenyl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine (**3h**)

Brown coloured solid, Yield (73%), M.p. 202–204 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 7.15–7.33 (m, 5H, H_{arom}), 7.65–7.72 (m, 5H, H_{arom} and s, 1H buried C-4H), 8.22–8.28 (m, 4H, H_{arom}), 8.52 (bs, 1H, NH); ^{13}C NMR: δ 158 (C-3, 7, 5a and 10a),134 (C-4‴), 142 (C-4⁗), 137 (C-4″), 130 (C-4′), 129 (C-1′, 1″, 1⁗), 128 (C-3′,3″,3⁗ 5″, 5‴, 5′), 127 (C-2′, 6′, 2″, 2‴, 6″, 6‴), 77 (C-3a), 41 (CH_2), 28(CH_3); IR (ν_{max} in cm^{-1}, KBr): 3080, 3032, 1625, 1440, 1404. *Anal. Calcd*. for $C_{24}H_{16}N_8O_2$: C, 64.28; H, 3.57; N, 25.60; O, 7.14. Found: C, 64.24; H, 3.54; N, 25.59; O, 7.12. *m*/*z*(%) = 448 (M^+)

6.9. N-(4‴-Nitrophenyl)-8-benzyl-3-phenyl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine (**3i**)

Brown coloured solid, Yield (72%), M.p. 200–202 °C .^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 4.05 (s, 12H, Ar-CH_2), 7.10–7.32 (m, 10H, H_{arom}), 7.58–7.62 (m, 2H, H_{arom}), 7.69 (s, 1H, C-4H), 8.12–8.18 (m, 2H, H_{arom}), 8.58 (bs, 1H, NH); ^{13}C NMR: δ 158 (C-3, 7, 5a and 10a),134 (C-4‴), 142 (C-4⁗), 137(C-4″), 130 (C-4′), 129 (C-1′, 1″, 1⁗), 128 (C-

3′,3″,3‴′ 5″, 5‴′, 5′), 127 (C-2′, 6′, 2″, 2‴, 6″, 6‴), 77 (C-3a), 41 (CH_2), 28(CH_3); IR (ν_{max} in cm^{-1}, KBr): 3101, 3030, 2925, 1610, 1475, 1410. *Anal. Calcd*. for $C_{25}H_{18}N_7O_2$: C, 67.56; H, 4.05; N, 21.17; O, 7.20. Found: C, 67.54; H, 4.03; N, 21.15; O, 7.18. $m/z(\%) = 444$ (M^+).

*6.10. N-(4‴-Nitrophenyl)-8-(4′-nitrophenyl)–3-phenyl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine (**3j**)*

Brown coloured solid, Yield (76%), M.p. 180–182 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 7.18–7.32 (m, 4H, H_{arom}), 7.39–7.50 (m, 3H, H_{arom}), 7.62–7.68 9m, 2H, H_{arom} and s, 1H buried C-4H, 8.10–8.20 (m, 4H, H_{arom}), 8.40 (bs, 1H, H_{arom}); ^{13}C NMR: δ 158 (C-3, 7, 5a and 10a),134 (C-4‴), 142 (C-4‴), 137(C-4″), 130 (C-4′), 129 (C-1′, 1″, 1‴′), 128 (C-3′,3″,3‴′ 5″, 5‴′, 5′), 127 (C-2′, 6′, 2″, 2‴, 6″, 6‴), 77 (C-3a), 41 (CH_2), 28(CH_3); IR (ν_{max} in cm^{-1}, KBr): 3180, 3028, 1622, 1460, 1412. *Anal. Calcd*. for $C_{24}H_{15}N_9O_4$: C, 58.41; H, 3.04; N, 25.55; O,12.98. Found: C, 58.39; H, 3.01; N, 25.52; O, 12.95. $m/z(\%) = 493$ (M^+)

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