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Efficient synthesis of antifungal active 9-substituted-3-aryl-5*H*, 13*aH*-quinolino[3,2-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines in ionic liquids

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ABSTRACT

The title compounds, 9-substituted-3-aryl-5*H*,13*aH*-quinolino[3,2-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines **8**, are synthesized from 5-aryl-3,4-diamino-1,2,4-triazoles **5** and 2-chloro-3-formylquinolines **7** in ionic liquid as solvent under microwave heating as well as using oil-bath heating at 80 °C. The products are obtained in the good to moderate yields and in high purity. These compounds have been screened for antifungal activity. The screening data indicate that the compounds **8a**, **8b**, **8c** and **8d** show excellent activity against *Aspergillus niger* 1000 μg concentration and *Pencillium notatum* species at 500 μg as well as 1000 μg concentrations whereas, these compounds show good to moderate activity against *Aspergillus flavus* and *Rhizopus* species at both the concentrations. Moreover, ionic liquid is found to be recyclable for at least three consecutive runs what makes the process cost-effective and economic that lead to the area of *Green Chemistry* as recyclability is one of the most important feature of Green Chemistry.

Room-temperature ionic liquids[1] are gaining academic and industrial world wide attention,[2] as these can be used to replace the organic solvents in catalysis,[3] synthesis,[4,5] and separations.[6] The unique properties of RTILs enable their use as alternative solvents and may speed the introduction of potentially 'green' solvents into sustainable industrial processes. Heterocyclic compounds are highly essential to life as they play a vital role in metabolism of all living cells. Many heterocyclic compounds containing N, O and S show wide range of physiological activities. Hence, they are claimed as potential biologically active compounds. For instance, a number of pyrazole derivatives are associated with wide range of biological activities such as antifungal[7] and antibacterial[8]. Triazole derivatives are known to possess antifungal,[9] antibacterial,[10] anti-inflammatory,[11] antimicrobial[12,13] and antiasthamatic[14,15] activities while thiadiazepine derivatives have reported to exhibit wide range of biological activities such as herbicidal, antimicrobial, antiinflammatory and analgesics.

Some recent examples[16–22] have been reported in the literature which show that antifungal active compounds occupy a unique position in pharmacological kingdom.

To study the combined effect of these three heterocyclic moieties in a single network, there is a continued interest in the synthesis of 9-substituted-3-aryl-5*H*,13*aH*-quinolino[3,2-*f*][1,2,4]triazolo 4,3-*b*][1,2,4]triazepines **8**. Various ionic liquids such as 1-butyl-3-methyl imidazolium tetrafloroborate, imidazolium, pyridinium, piperidinium and morpholinium have been reported in the literature which are used as efficient catalysts and solvents in organic synthesis.[23–26] These ionic liquids have been found to be superior to the classical solvents used for preparation of triazepines.[27–30] Keeping in view the importance of reported ionic liquids, we have tried to synthesize a new class of ionic liquids, that is, 1,3,5-trimethylpyrazoliumtetrafluoroborate ionic liquid (**10**) (Scheme 4) and are able to get 85% yield. In recent years, microwave activation couple efficiently with solid supports and represent an environment-friendly methodology. Further, work-up procedure is simply reduced to filtration followed by washing with water. Moreover, products are obtained in a state of high purity. In this Letter, we report the simple preparation of novel 1,3,5-trimethylpyrazolium tetrafluoroborate (**10**) (Scheme 4) and its application in the synthesis of antifungal active compounds 9-substituted-3-aryl-5*H*,13*aH*-quinolino[3,2-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines using ionic liquid under microwave irradiation (Scheme 4). In this case, novel 1,3,5-trimethylpyrazoliumtetrafluoroborate (**10**) (Scheme 4) is studied as solvent. Moreover, the novel 1,3,5-trimethylpyrazoliumtetrafluoroborate is found to be re-cyclable for at least three runs without loss of much activity rendering the process more economic.

The required precursor, 5-aryl-3,4-diamino-1,2,4-triazoles **5**,[31] were prepared from methyl benzoates **1** which were then converted to aroyl hydrazides **2**[32] on refluxing with hydrazine hydrate in ethanol followed by conversion to aroyl thiosemicarbazides **3**[33] on heating with potassium thiocyanate in aq HCl. Aroyl thiosemicarbazides were then converted to 2-amino-5-aryl-1,3,4-thiadizoles[34] **4** which were then converted to 5-aryl-3,4-diamino-1,2,4-triazoles **5** on refluxing with hydrazine hydrate in ethanol as

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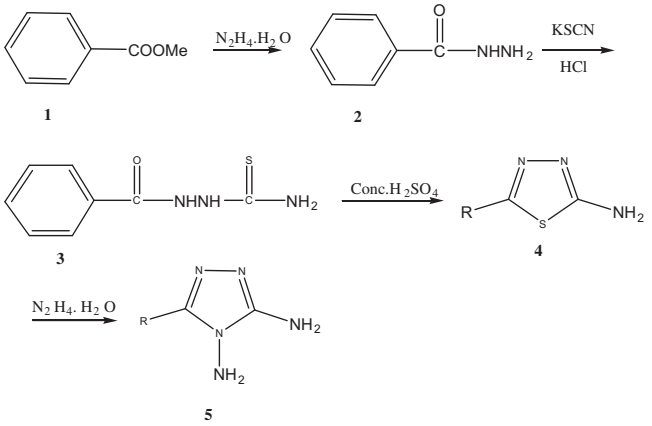
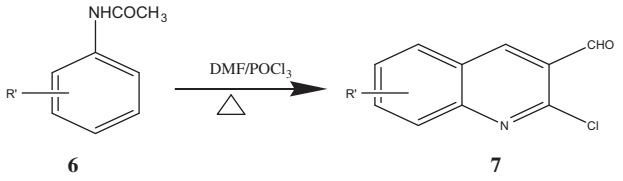


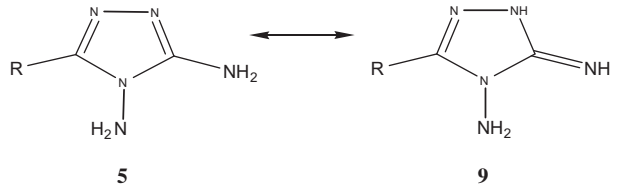
Scheme 1. R = C_6H_5, 2-ClC_6H_4, 4-ClC_6H_4, $CH_2C_6H_5$, (4-NO_2)C_6H_4.

shown in Scheme 1, while 2-chloro-3-formyl quinolines **7**,[35] were prepared by Vilsmeir Haack reaction of acetanilides/substituted acetanilides **6** as illustrated in Scheme 2. The synthesized precursors were then used for the synthesis of title compounds **8a–j** in the presence of ionic liquid under both microwave and oil-bath heating.

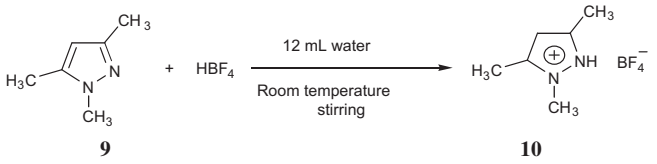
It was found that ionic liquid has not yet been used for the condensation of 2-chloro-3-formyl quinolines **7** with 5-aryl-3,4-diamino-1,2,4-triazoles **5** followed by cyclisation to afford 9-substituted-3-aryl-5*H*,13*aH*-quinolino[3,2-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines **8** which is outlined in Scheme 5. While carrying out the reaction, it was found that the two amino groups were present at 4 and 5-position of 5-aryl-3,4-diamino-1,2,4-triazole **5** but the amino group at C-5 position was involved in tautomerisation giving tautotmeric form as shown in Scheme 3. It was supported by the fact that only –C–NH_2 group can form Schiff's base with 2-chloro-3-formyl quinolines **7** while H_2N–N– group containing compounds are analogues to hydrazino type compounds which can displace chlorine easily of 2-chloro-3-formyl quinolines **7**. So, it was only the amino group at C-2 position of 5-aryl-3,4-diamino-1,2,4-triazole **5** which can form Schiff's base with 2-chloro-3-formyl quinolines **7** while N–NH_2 of **5** cannot form Schiff's base. Moreover, in the resulting product **8**, the H-atom at 5-position (NH) can form hydrogen bond with all the 'R' groups present at C-3 position. Free amino group can displace chlorine easily while imino group cannot displace chlorine easily. These are the evidences which support that displacement occurs via NH_2–N– and condensation occurs via –C–NH_2.



Scheme 2. R = 4-CH_3, 3-CH_3, 4-OMe.



Scheme 3.



Scheme 4.

The reaction of 5-phenyl-3,4-diamino-1,2,4-triazole **5a** with 2-chloro-3-formyl quinoline was tried in ionic liquid and isolated **8a** in 70% yield. Similar reaction was also carried out with different substrates under conventional conditions at 80 °C and was able to isolate 58% yield. To check the generality of the reaction, this procedure was also applied to other substrates and found good to moderate yields. The results are summarised in Table 1. Thus, this represents a rapid, mild, cost-effective and green procedure for the synthesis of 9-substituted-3-aryl-5*H*,13*aH*-quinolino[3,2-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines.

In order to optimise the reaction conditions, different reactions were tried with varying amount of 2-chloro-3-formylquinolines **7a** and 5-phenyl-3,4-diamino-1,2,4-triazole **5a** which were selected as test substrates. It was found that for 5 mmole of each of 5-phenyl-3,4-diamino-1,2,4-triazole **5a**, 2-chloro-3-formylquinoline **7a**, 1 ml of ionic liquid was required under microwave heating and as solvent under oil-bath heating to give maximum yield under mild conditions. To select the optimum power level, reaction with test substrates was carried out at different power levels from 80 to 900 W. It was found that 640 W was selected as the optimum power level as far as yield and reaction times are concerned. At low power level, the reaction remains incomplete whereas, at high power level, low yields of products were obtained which may be due to decomposition. Under oil-bath hating, 80 °C was selected as the optimum reaction temperature.

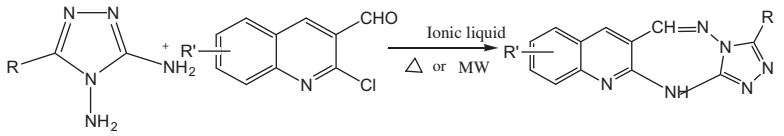
Some of the synthesized compounds were screened for antifungal activity against *Aspergillus flavus*, *Aspergillus niger*, *Rhizopus* species and *Pencillium notatum* species by paper disc technique against two concentrations 500 μg/ml and 1000 μg/ml. The zone of inhibition after 24 h of incubation at 28 ± 2 °C was compared with that of standard fluconazole. The screening data indicated that the compounds **8a**, **8b**, **8c** and **8d** showed excellent activity against *A. niger* 1000 μg concentration and *P. notatum* 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.

Preparation of the medium: Potato dextrose agar-agar medium 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 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 sterilized in pressure cooker for 30 min and few drops of streptomycin were added to prevent it from any bacterial contamination.



5 7 8

8a: R= C_6H_5, R'= H
8b:R= $(NO_2)C_6H_4$, R'= H
8c : R= 2-ClC_6H_4, R'= 3-CH_3
8d:R= (4-NO_2)C_6H_4, R'= 3-CH_3
8e: R= 2-ClC_6H_4, R'= 4-OCH_3
8f:R= $CH_2C_6H_5$, R'= 4-CH_3
8g: R= C_6H_5, R'= 4-CH_3
8h: R= 4-ClC_6H_4,R'= 4-OCH_3
8i: R= (4-NO_2)C_6H_4, R'= 4-OCH_3
8j:R= (4-NO_2)C_6H_4, R'= 4-CH_3

Scheme 5. **8a**: R = C_6H_5, R′ = H; **8b**: R = $(NO_2)C_6H_4$, R′ = H; **8c**: R = 2-ClC_6H_4, R′ = 3-CH_3; **8d**: R = (4-NO_2)C_6H_4, R′ = 3-CH_3; **8e**: R = 2-ClC_6H_4, R′ = 4-OCH_3; **8f**: R = $CH_2C_6H_5$, R′ = 4-CH_3; **8g**: R = C_6H_5, R′ = 4-CH_3; **8h**: R = 4-ClC_6H_4,R′ = 4-OCH_3; **8i**: R = (4-NO_2)C_6H_4, R′ = 4-OCH_3; **8j**: R = (4-NO_2)C_6H_4, R′ = 4-CH_3.

Table 1
Physical data of synthesized compounds 9-substituted-3-aryl-5*H*,13*aH*-quinolino[3,2-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines in ionic liquid

Compound	Microwave (MW)		Oil-bath heating at 8 °C (Δ)		Mp (°C)
	Time (min)	Yield (%)	Time (h)	Yield (%)	
8a	4	70[a]	21	58[a]	160–162
8b	3	78[b]	12	66[b]	210–212
8c	7	68 [a]	20	65[a]	172–174
8d	4	72[a]	10	62[a]	204–206
8e	11	80[b]	20	70[b]	220–222
8f	5	70[a]	26	62[a]	210–212
8g	6.5	78[a]	23	65[a]	214–216
8h	7.5	85[a]	20	70[a]	215–217
8i	5	80[a]	9	76[a]	138–140
8j	8	74[a]	11	60[a]	190–192

[a] Products were purified by crystallisation from ethyl acetate.
[b] Products were purified by passing through column of alumina and elution with ethyl acetate/petroleum ether.

Table 2
Antifungal activity of synthesized compounds 9-substituted-3-aryl-5*H*,13*aH*-quinolino[3,2-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines

S. No.	Compd No. Concn (μg/ml)	Zone of inhibition in mm (%)							
		Aspergillus niger		*Aspergillus flavus*		*Rhizopus* species		*Pencillium notatum* species	
		500 μg	1000 μg	500 μg	1000 μg	500 μg	1000 μg	500 μg	1000 μg
1	**8a**	39 (53.33)	43 (71.66)	32 (53.33)	45 (70.00)	30 (50.00)	30 (50.00)	44 (73.33)	54 (90.00)
2	**8b**	22 (33.33)	38 (63.33)	36 (60.00)	36 (60.00)	25 (41.66)	26 (43.33)	43 (71.66)	52 (86.66)
3	**8c**	24 (40.00)	43 (71.66)	42 (70.66)	32 (53.33)	28 (46.66)	32 (53.33)	44 (73.33)	42 (70.00)
4	**8d**	34 (56.66)	40 (66.66)	43 (71.66)	49 (81.66)	20 (33.33)	30 (50.00)	48 (80.00)	42 (70.00)
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)

Procedure: Potato dextrose medium was prepared and sterilized in pressure cooker for 30 min. Sterilized 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, P. notatum* 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 Whatmann 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 ± 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 and 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.

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 immune compromised. 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 standardised 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.

Experimental Section: General. All the 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 spectrophotometer. The mass spectral data was obtained on a JEOL JMS-D 300 spectrometer. The elemental analysis was performed on a simple CHNS-932 Analyser (Leco). The reactions were carried out in domestic microwave oven LG-MS-255R with maximum output power of 900 W and by using pre-heated oil-bath.

*General procedure for the synthesis of compounds **8a–j**: Microwave heating.* A mixture of 5-phenyl-3,4-diamino-1,2,4-triazole **5** (5 mmol), 2-chloro-3-formylquinoline **7** (5 mmol), ionic liquid (1 ml) was taken in a 50 ml borosil beaker and mixed properly with the help of a glass rod (5 s). The mixture was then exposed to microwave irradiation for an appropriate time (monitored by TLC, shown in Table 1) followed by cooling time of 5 s each at 640 W. After the completion of reaction, petroleum ether was added and it was found that ionic liquid settled at the bottom. It was then decanted off. The crude product was purified either by crystallisation from ethyl acetate or by passing through a column of alumina and elution with ethylacetate and petroleum ether.

The physical data of the synthesized compounds is given in Table 1. The structures of the products were confirmed by IR, ^{1}H NMR, mass spectral data and elemental analysis.

Oil-bath heating. A mixture of 5-phenyl-3,4-diamino-1,2,4-triazole **5** (5 mmol), 2-chloro-3-formylquinoline **7** (5 mmol), ionic liquid (1 ml) was taken in a 50 ml in a round bottomed flask. The reaction mixture was stirred in oil-bath at 80 °C for the appropriate time (monitored by TLC, shown in Table 1). After the completion of reaction, petroleum ether was added and it was found that ionic liquid settled at the bottom. It was then decanted off. The crude product was purified either by crystallisation from ethyl acetate or by passing through a column of alumina and elution with ethylacetate and petroleum ether.

The physical data of the synthesized compounds is given in Table 1. The structures of the products were confirmed by IR, ^{1}H NMR, mass spectral data and elemental analysis.

Recyclability of ionic liquid: 1,3,5-Trimethylpyrazolium tetrafluoroborate was found to be recyclable for at least three runs. The reaction in case of entry 1 was carried out for three consecutive runs (1st run: 70% after 4 min; 2nd run: 69% after 6 min.; 3rd run: 67% after 9 min.) with the same ionic liquid. These results demonstrated that there was no significant loss of activity of ionic liquid as it was recyclable.

*Spectral data of the synthesized compounds **8a–j**: 3-Phenyl-5H,13aH-quinolino[3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine 8a.* This compound was obtained as orange coloured shining solid (ethyl acetate), mp 160–162 °C; IR (KBr, ν_{max} in cm^{-1}): 3100 (NH), 3040 (aromatic C–H), 1642 (C=N), 1406 (C–N); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 7.10–7.34 (m, 4H, H_{arom}), 7.47–7.69 (m, 5H, H_{arom} and s, 1H buried N=CH), 8.01 (d, 1H, H_{arom}), 8.35 (br s, 1H, H_{arom}); ^{13}CNMR ($CDCl_3$): δ 166 (C-11a, 5a), 164 (C-12), 160 (C-3,14), 133 (C-11), 132 (C-9), 131 (C-8), 130 (C-1′, 4′), 129 (C-2′, 6′), 128(C-3′, 5′), 126 (C-7, 10), 121 (C-10a, 6a); ms: m/z (M^+) 292.

Anal. Calcd for $C_{18}H_{12}N_6$: C, 73.97; H, 4.10; N, 21.91. Found: C, 73.93; H, 4.06; N, 21. 87.

*3-(4′-Nitrophenyl)-5H,13aH-quinolino[3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine **8b**.* This compound was obtained as brown coloured shining solid (through column), mp 210–212 °C; IR (KBr, ν_{max} in cm^{-1}): 3108 (NH), 3070 (aromatic C–H), 1638 (C=N), 1540 (NO_2), 1430 (C–N); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 7.20 (m, 1H, H_{arom}), 7.50–7.58 (m, 2H, H_{arom}), 7.70–7.85 (m, 3H, H_{arom} and s, 1H buried N=CH), 8.02 (d, 1H, H_{arom}), 8.20–8.31 (m, 2H, H_{arom}), 8.55 (br s, 1H, NH); ^{13}CNMR ($CDCl_3$): δ 166 (C-11a, 5a), 164 (C-12), 160 (C-3,14), 134 (C-1′, 4′), 133 (C-11), 132 (C-9), 131 (C-8), 130 (C-2′, 6′), 129 (C-3′, 5′), 126 (C-7, 10), 121 (C-10a, 6a); ms: m/z (M^+) 353.

Anal. Calcd for $C_{18}H_{11}N_7O_2$: C, 61.18; H, 3.11; N, 26.62; O, 9.06. Found: C, 61.14; H, 2.97; N, 26.58; O, 9.02.

*9-(3″-Methyl)-3-(2′-chlorophenyl)-5H,13aH-quinoloino[3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine **8c**.* This compound was obtained as yellow shining solid (through column), mp172–174 °C; IR (KBr, ν_{max} in cm^{-1}): 3120 (NH), 3040 (aromatic C–H), 2825 (C–H), 1620 (C=N), 1424 (C–N), 748 (C–Cl); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.30 (s, 3H, CH_3), 7.12–7.36 (m, 4H, H_{arom}), 7.45–7.58 (m, 3H, H_{arom}), 7.69 (s, 1H, N=CH), 7.98 (d, 1H, H_{arom}), 8.35 (br s, 1H, NH); ^{13}CNMR ($CDCl_3$): δ 166 (C-11a, 5a), 164 (C-12), 160 (C-3,14), 133 (C-11, 1′, 4′), 132 (C-9), 131 (C-8), 129 (C-2′, 6′), 128 (C-3′, 5′), 126 (C-7, 10), 121 (C-10a, 6a), 30 (CH_3); ms: m/z (M^+) 340.5.

Anal. Calcd for $C_{19}H_{13}N_6Cl$: C, 66.96; H, 3.81; N, 18.79; Cl, 9.86. Found: C, 66.92; H, 3.77; N, 18.72.

*9-(3″-Methyl)-3-(4′-nitrophenyl)-5H,13aH-quinolino-[3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine **8d**.* This compound was obtained as brown coloured shining solid (ethyl acetate), mp 204–206 °C; IR (KBr, ν_{max} in cm^{-1}): 3115 (NH), 3060 (aromatic C–H), 2810 (C–H), 1510 (NO_2), 1420 (C–N); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.32 (s, 3H, CH_3), 7.22 (m, 1H, H_{arom}), 7.52–7.68 (m, 1H, H_{arom} and s, 1H buried N=CH), 7.72–7.82 (m, 3H, H_{arom}), 8.16–8.28 (m, 2H, H_{arom}), 8.35 (br s, 1H, NH); ^{13}CNMR ($CDCl_3$): δ 166 (C-11a, 5a), 164 (C-12), 160 (C-3, 14), 134 (C-1′, 4′), 133 (C-11), 132 (C-9), 131 (C-8), 130 (C-2′, 6′), 129 (C-3′, 5′), 126 (C-7, 10), 121 (C-10a, 6a), 30 (CH_3); ms: m/z (M^+) 367.

Anal. Calcd for $C_{19}H_{13}N_7O_2$: C, 62.12; H, 3.54; N, 25.61; O, 8.73. Found: C, 61.98; H, 3.50; N, 25.50.

*9-(4″-Methoxy)-3-(2′-chlorophenyl)-5H,13aH-quinolino [3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine **8e**.* This compound was obtained as yellow coloured shining solid (ethyl acetate), mp 220–222 °C; IR (KBr, ν_{max} in cm^{-1}): 3120 (NH), 3080 (aromatic C–H), 1628 (C=N), 1434 (C–N), 1225 (OCH_3), 738 (C–Cl); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.95 (s, 3H, OCH_3), 7.15–7.34 (m, 4H, H_{arom}), 7.42–7.60 (m, 3H, H_{arom}), 7.60 (s, 1H, N=CH), 7.97 (d, 1H, H_{arom}), 8.35 (br s, 1H, NH); ^{13}CNMR ($CDCl_3$): δ 166 (C-11a, 5a), 164 (C-12), 160 (C-3,14), 133 (C-11, 1′, 4′), 132 (C-9), 131 (C-8), 129 (C-2′, 6′), 128 (C-3′, 5′), 126 (C-7, 10), 121 (C-10a, 6a), 60 (OCH_3); ms: m/z (M^+) 356.5.

Anal. Calcd for $C_{19}H_{13}N_6OCl$: C, 63.95; H, 3.64; N, 17.95; Cl, 9.42; O, 4.91 Found: C, 63.91; H, 3.60; N, 17.91; O, 4.90.

*9-(4″-Methyl)-5-benzyl-3H,13aH-quinolino[3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine **8f**.* This compound was obtained as yellow coloured shining solid (through column), mp 210–212 °C; IR (KBr, ν_{max} in cm^{-1}): 3120 (NH), 3030 (aromatic C–H), 1640 (C=N), 1421 (C–N); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.34 (s, 3H, CH_3), 4.04 (s, 2H,

Ar-CH_2), 7.09–7.28 (m, 4H, H_{arom}), 7.45–7.60 (m, 4H, H_{arom}), 7.68 (s, 1H, N=CH), 8.01 (d, 1H, H_{arom}), 8.35 (br s, 1H, NH); ^{13}CNMR ($CDCl_3$): δ 166 (C-11a, 5a), 164 (C-12), 160 (C-3, 14), 133 (C-11, 1′, 4′), 132 (C-9), 131 (C-8), 129 (C-2′, 6′), 128 (C-3′, 5′), 126 (C-7, 10), 121 (C-10a, 6a), 41 (CH_2) 30(CH_3); ms: *m*/*z* (M^+) 340.

Anal. Calcd for $C_{20}H_{16}N_6$: C, 70.58; H, 4.70; N, 24.70. Found: C, 70.52; H, 4.65; N, 24.78.

9-(4″-Methyl)-5-phenyl-3H,13aH-quinolino-[3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine ***8g***. This compound was obtained as pale yellow shining solid (ethyl acetate), mp 214–216 °C; IR (KBr, ν_{max} in cm^{-1}): 3110 (NH), 3022 (aromatic C–H),2810 (C–H), 1640 (C=N), 1406 (C–N); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.34 (s, 3H, CH_3), 7.11–7.34 (m, 4H, H_{arom}), 7.43–7.65 (m, 4H, H_{arom}), 7.70 (s, 1H, N=CH), 8.02 (d, 1H, H_{arom}), 8.31 (br s, 1H, H_{arom}); ^{13}CNMR ($CDCl_3$): δ 166 (C-11a, 5a), 164 (C-12), 160 (C-3,14), 133 (C-11, 1′, 4′), 132 (C-9), 131 (C-8), 129 (C-2′, 6′), 128 (C-3′, 5′), 126 (C-7, 10), 121 (C-10a, 6a), 30 (CH_3); ms: *m*/*z* (M^+) 306.

Anal. Calcd for $C_{19}H_{14}N_6$: C, 68.78; H, 4.45; N, 26.75. Found: C, 68.74; H, 4.41; N, 26.71.

9-(4″-Methoxy)-5-(4′-chlorophenyl)-3H,13aH-quinolino-[3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine ***8h***. This compound was obtained as pale yellow shining solid (ethyl acetate), mp 215–217 °C; IR (KBr, ν_{max} in cm^{-1}); 3110 (NH), 3042 (aromatic C–H), 1612 (C=N), 1428 (C–N), 1275 (OCH_3), 759 (C–Cl); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.92 (s, 3H, OCH_3), 7.11–7.36 (m, 3H, H_{arom}), 7.39–7.57 (m, 4H, H_{arom}), 7.70 (s, 1H, N=CH), 8.01 (d, 1H, H_{arom}), 8.30 (br s, 1H, NH); ^{13}CNMR ($CDCl_3$): δ 166 (C-11a, 5a), 164 (C-12), 160 (C-3, 14), 133 (C-11, 1′, 4′), 132 (C-9), 131 (C-8), 129 (C-2′, 6′), 128 (C-3′, 5′), 126 (C-7, 10), 121 (C-10a, 6a), 60 (OCH_3); ms: *m*/*z* (M^+) 356.5.

Anal. Calcd for $C_{19}H_{13}N_6OCl$: C, 63.95; H, 3.64; N, 17.95; O, 0.03; Cl, 9.95. Found: C, 63.90; H, 3.60; N, 17.90; O, 0.02.

9-(4″-Methoxy)-5-(4′-nitrophenyl)-3H,13aH-quinolino[3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine ***8i***. This compound was obtained as yellow coloured shining solid (through column), mp 138–140 °C; IR (KBr, ν_{max} in cm^{-1}): 3100 (NH), 3020 (aromatic C–H), 1640 (C=N), 1442 (C–N), 1440 (NO_2), 1275 (OCH_3); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.92 (s, 3H, OCH_3), 7.22 (m, 1H, H_{arom}), 7.60–7.72 (m, 1H, H_{arom} and s, 1H buried N=CH), 7.75–7.86 (m, 3H, H_{arom}), 7.99 (d, 1H, H_{arom}), 8.21–8.24 (m, 2H, H_{arom}), 8.36 (br s, 1H, H_{arom}); ^{13}CNMR ($CDCl_3$): δ 166 (C-11a, 5a), 164 (C-12), 160 (C-3, 14), 134 (C-1′, 4′), 133 (C-11), 132 (C-9), 131 (C-8), 129 (C-2′, 6′), 128 (C-3′, 5′), 126 (C-7, 10), 121 (C-10a, 6a), 60 (OCH_3); ms: *m*/*z* (M^+) 387.

Anal. Calcd for $C_{19}H_{13}O_3N_7$: C, 58.91; H, 3.35; N, 25.32, O, 12.42. Found: C,58.87; H,3.32; N, 25.31. O, 12.40.

9-(4″-Methyl)-5-(4′-nitrophenyl)-3H,13aH-quinolino-[3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine ***8j***. This compound was obtained as brown coloured shining solid (through column), mp 190–192 °C; IR (KBr, ν_{max} in cm^{-1}); 3122 (NH), 3044 (aromatic C–H), 1620 (C=N), 1470 (NO_2), 1428 (C–N), ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.34 (s, 3H, CH_3), 7.25 (m, 1H, H_{arom}), 7.53–7.69 (m, 1H, H_{arom} and s, 1H buried N=CH), 7.712–7.85 (m, 3H, H_{arom}), 8.01 (d,1H, H_{arom}), 8.15–8.30 (m, 2H, H_{arom}), 8.38 (br s, 1H, NH); ^{13}CNMR ($CDCl_3$): δ 166 (C-11a, 5a), 164 (C-12), 160 (C-3, 14), 134 (C-1′, 4′), 133 (C-11), 132 (C-9), 131 (C-8), 129 (C-2′,6′), 128 (C-3′, 5′), 126 (C-7, 10), 121 (C-10a, 6a), 30 (CH_3); ms: *m*/*z* (M^+) 371.

Anal. Calcd for $C_{19}H_{13}N_7O_2$: C, 61.45; H, 3.50; N, 26.41; O, 8.64. Found: C, 61.35; H, 3.42; N, 26.38; O, 8.60.

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References and notes

1. Seddon, K. R. *J. Chem. Tech. Biotechnol.* **1997**, *68*, 351.
2. Bradley, D. *Chem. Ind.* **1999**, *86*, 445.
3. Welton, T. *Chem. Rev.* **1999**, *99*, 2071.
4. Blanchard, L.; Hancu, D.; Beckmann, E. J.; Brennecke, J. F. *Nature* **1999**, *399*, 28.
5. Dai, S.; Ju, Y. H.; Barner, C. E. *J. Chem. Soc., Dalton Trans.* **1999**, 1201.
6. Hudelston, J. G.; Willauer, H. D.; Swatloski, R. P.; Visser, A. E.; Rogers, R. D. *Chem. Commun.* **1998**, 1765.
7. Cliford, D. P.; Jackson, D. P.; Edwards, K. V.; Jeffrey, P. *Pestic. Sci.* **1976**, *7*, 453.
8. Hu, C.-C.; Yan, Z.; Zhang, Z.-Y.; Chun, L.-Z.; Ren, L. *Indian J. Chem.* **2000**, *29B*, 791.
9. Udupi, R. H.; Purushottam, P.; Bhat, A. R. *Indian J. Chem., Sect. B* **2000**, *39*, 291.
10. Shafiee, A.; Tabatabaiee, M. *J. Chem. Eng.* **1998**, *17*, 14.
11. Mulwad, V. V.; Pawa, R. B. *Indian J Chem., Sect. B* **2003**, *42*, 2901.
12. Kidwai, M.; Bala, S.; Mishra, A. D. *Indian J. Chem., Sect. B* **2004**, *43*, 2485.
13. Ogura, A. H.; Takahashi, I. H. Japan Kokai Tokkyo Koho, Japan Patent 76,39,685; *Chem. Abstr.* **1977**, *86*, 5765.
14. Salerno, A.; Ceriani, V.; Perillo, I. *J. Heterocycl. Chem.* **1992**, *29*, 1725.
15. Cherney, R. J.; Duan, J. J.-W.; Voss, M. E.; Chen, L.-C.; Wang, D. T.; Meyer, Z. R.; Wasserman, K. D.; Hardman, R.-Q.; Liu, M. B.; Qian, M. S.; Mandlakar, D. D.; Christ, J. M.; Trazaskos, R. C.; Newton, R. L.; Megolda, R. R.; Decicco, C. P. *J. Med. Chem.* **2003**, *46*, 1811.
16. Dhanasekaran, D.; Thajuddin, N.; Panneerselvam, A. *Med. Biol.* **2008**, *15*, 7.
17. Shahid, M.; Shahzad, M.; Tripathi, T.; Sobia, F.; Singh, A.; Malik, A.; Shutalluh, F.; Khan, H. *Anti-Infect. Agents Med. Chem.* **2009**, *8*, 36.
18. Hsein, P.; Lee, C.-W.; Chou, J. Y.; Sneih, B.-J.; Chen, H.-M. *Bioresour. Technol.* **2007**, *98*, 232.
19. Masoko; Eloff, J. N. *Afr. J. Biotechnol.* **2006**, *5*, 1625.
20. Bhoot, D. P.; Khunt, R. C.; Shankhavara, V. K.; Parekh, H. H. *J. Sci. Islamic Repub. Iran* **2006**, *17*, 323.
21. Prasad, N.; Vivek, M. N.; Ashwini Prasad, H. K.; Shruthi, T.; Shankara Bhat, S.; Nagaraja, G. K.; Swamy, S. N. *J. Chem. Pharm. Res.* **2010**, *2*, 67.
22. Zanoni, M. V. B.; Rogers, E. I.; Hardacre, C.; Compton, R. G. *Int. J. Electrochem. Sci.* **2009**, *4*, 1607.
23. Maradolla, M. B.; Allam, S. K.; Mandha, A.; Chandramouli, G. V. P. *ARKIVOC* **2008**, 42.
24. Hajipour, A. R.; Rafiee, F. *J. Iran Chem. Soc.* **2009**, *6*, 647.
25. Romanelli, G. P.; Autino, J. C. *Mini-Rev. Org. Chem.* **2009**, *6*, 359.
26. Mallakpour, S.; Kolahdoozan, M. *Polym. J.* **2008**, *40*, 513.
27. Ait Itto, M. Y.; Hasnaoui, A.; Riahi, A.; Lavergne, J.-P. *Tetrahedron Lett.* **1997**, *38*, 2087.
28. Aitali, M.; Itto, M. Y. A.; Hasnaoui, A.; Riahi, A.; Karima, A.; Daran, J.-C. *J. Organomet. Chem.* **2001**, *619*, 265.
29. Abdel Mgeid, M. *Chem. Heterocycl. Compd.* **2009**, *45*, 1888.
30. Srinivas Reddy, G.; Kumar, P. A.; Anand, R.; Mukkanti, K.; Reddy, P. P. *Synlett* **2009**, 1463.
31. Padhy, A. K.; Nag, V. L.; Panda, C. S. *Indian J. Chem., Sect. B* **1999**, *38*, 998.
32. Shanker, K.; Aggarwal, V. K.; Selveraj, R. J.; Parmar, S. *J. Med. Chem.* **1969**, *12*, 324.
33. Andreith, L. F.; Scott, E. S.; Kipper, P. S. *J. Org. Chem.* **1954**, *19*, 733.
34. *Vogel's Text Book of Practical Organic Chemistry Including Qualitative Organic Analysis*, 3rd ed., E. L. B. S and Longman Group, Ltd: London, 1973; p 781.
35. Cohn, M.; Narme, B.; Tarnovski, B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1525.