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Synthesis and antifungal evaluation of imines derived from 3-Amino-2-isopropyl-3H-quinazolin-4-one

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Abstract: Novel Schiff bases were synthesised using 3-aminoquinazolinone (**1**) and a variety of aldehydes in the presence of acetic acid as solvent. Antifungal evaluation of the compounds was carried out by the agar dilution method. Among the all compounds prepared, quinazolinone itself showed the best fungiostatic activity against all filamentous fungi.

Keywords: Quinazolinone; schiff bases; Imines; antifungal; antimicrobial.

1. Introduction

A wide variety of quinazolinone-based alkaloid natural and non-natural products have been known for their biological properties, for example, antitumor,[1-4] anti-inflammatory,[5-7] anticonvulsant,[8-11] analgesic,[6,7,12] as well as anti-HIV.[13-15] For this reason, total synthesis of naturally occurring quinazolinones e.g. Vasicinones,[16-19] Fumiquinazolinones,[20-24] Luotonins,[25] Circumdatin[26-28] and Asperlicin[29,30] have earlier been reported. Additionally, due to pharmacological importance, attentions have also been paid to synthesis of novel quinazolinone-based derivatives. A novel and practical method 2,3-disubstituted quinazolinones was accounted using microwave chemistry[26,31,32] and solid-phase synthesis.[33-38]

The indiscriminate use of antibiotics is going through a crisis due to the rapidly increasing development of bacterial resistant strains to existing agents. The emerging resistance of microorganisms to some antibiotics makes it necessary to continue to search for newer and more effective and less expensive antimicrobial substances. Therefore, increasing interest has also focused on the antimicrobial potential of the quinazolinone derivatives. The antimicrobial properties of

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quinazolinone derivatives are established against several microorganisms including bacteria, yeasts and fungi.[39-45]

We screened and found promising results with a number 3-aminoquinazolinones with a known structures against microorganisms (unpublished results), therefore, we aim at this work is to synthesis of some novel quinazolinone derivatives and to search for their antifungal potentialities.

2. Results and Discussion

2.1.Chemistry: One of the more important reason for our interest in 3-aminoquinazolinone[46] (**1**) relates to the possibility of condensation of the amine group in its structure with more feasibility that useful lactamisation process generated at this position. According to the procedure of Barker,[47] 3-amino-2-isopropyl-3H-quinazolin-4-one (**1**) was synthesised starting from isobutyric anhydride and methyl anthranilate in 42% overall yield. Afterwards, 3-aminoquinazolinone (**1**) and benzaldehyde was refluxed in ethanol as solvent by a couple of drops of a variety of acids (AcOH, HCl and H_2SO_4), however, more than one products monitored by TLC. Consequently, we then changed our condition using acetic acid as solvent by heating at reflux temperature, a single product and excess of the benzaldehyde was visible under the UV lamp. The scope of the reaction of 3-amino-2-isopropyl-3H-quinazolin-4-one (**1**) with a series of aldehydes (showed in Table 1) was examined with the objective of obtaining biologically active compounds. After removing of excess acetic acid from the crude products, $NaHSO_3$ solution added and stirred for 15 minutes to remove excess aldehydes and extracted with dichloromethane afforded white crystalline solids in excellent purity and acceptable product yields (Scheme 1 and Table 1). All synthesised imines are novel except benzaldehyde derivative **2**.[46] The structure elucidation of the all Schiff Bases **(2-10)** was established that on the basis of their ^{1}H NMR, ^{13}C NMR, IR spectra. In all ^{1}H NMR spectra of the products, characteristic proton signal belongs to imines (N=C*H*) was appeared at between 8.35 and 9.48 ppm as singlets and doublets which are clearly assignable and agreeable. Elemental analysis results are also in agreement with ± 0.4 values (See experimental). Moreover, we consider and expecting to achieve β-lactam and quinazolinone ring systems (**11**) could be more potent for pharmacological activity, e.g. 3-amino-2-ethylquinazolinone derived lactam found potent for Antiparkinson disease,[48,49] thus, attempting made under the same literature procedure, lactamising the benzaldehyde-derived imine **2** (R=Ph) with intermediate chloroketene formed using chloroacetyl chloride and Et_3N in DMF, results by failure (Figure 1).

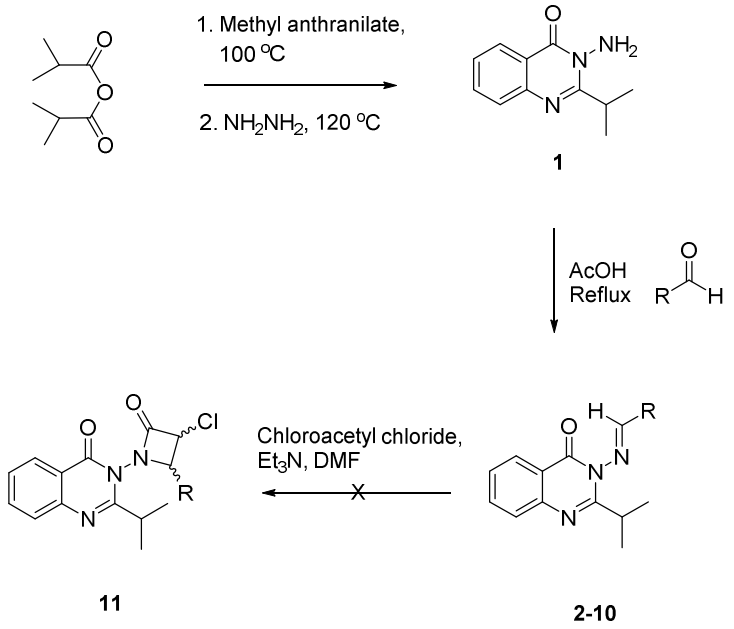
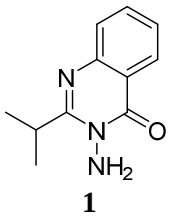
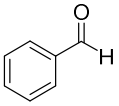
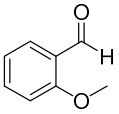
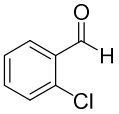
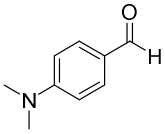
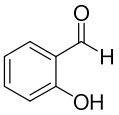
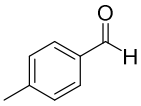
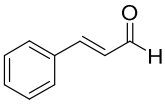
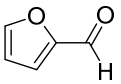
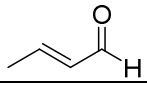


Figure 1. Lactamising the benzaldehyde-derived imine **2** (R=Ph) with intermediate chloroketene

Table 1. Result of Schiff Bases



1

Aldehydes	*Products*	*Yields %*[a]	*mp (°C)*
	**2**	77	129-131 (lit. 145)[46]
	**3**	82	116-118
	**4**	68	121-123
	**5**	69	203-205
	**6**	71	128-130
	**7**	82	134-135
	**8**	66	135-136
	**9**	44	114-116
	**10**	50	103-104

[a]Isolated yields after crystallisation

2.2.Biology: Antifungal activity of the compounds was carried out with the agar dilution method. [50] The assay was determined on Potato Dextrose Agar (PDA) plates included five concentrations of the test compound (1, 0.5, 0.25, 0.125 and 0.0625 mg/ml). The plates were left to stand overnight after pouring in a sterile condition to remove the solvent. Control containing chloroform was carried out in parallel. Suspension of spores from fungal strains was prepared by washing the slant agar with sterile saline solution and adjusted to 10^9 spores/ml. An inoculum of 5 µl of the spore suspension was added onto the centre of each agar plate. The plates were incubated for 72 h at 25 ºC. The diameters of mycelial growth (colony diameter, mm) in all plates were measured 3 days after incubation. Mycelial inhibition was calculated as the percentage of inhibition of radial growth relative to the control using the following formulae[50].

$$\%\ inhibition = \frac{\text{mycelial growth in control} - \text{mycelial growth in tested compound}}{\text{mycelial growth in control}} \times 100$$

Compounds that could not inhibit the mycelial growth of fungi up to a concentration of 1 mg/ml were considered inactive. Results from the screening of active test compounds against test fungi are given in Table 1, 2, 3 and 4. Compounds (**1**-**3**, **5, 6, 8**- **10**) inhibit the mycelial growth of *F. proliferatum*. Similarly, some compounds (**1**-**3**, **5**, **6**, **8** and **10**) were also active in inhibiting the mycelial growth of *A. parasiticus*. Only three compounds (**1**, **3** and **8**) were active against the mycelial growth of *A. niger*. Inhibitory activity against the mycelial growth of *T. reseii* was shown using the compounds **1**, **3**, **7** and

10. Among the active test compounds, 3-aminoquinazolinone **1** itself, gave the best results in inhibiting the mycelial growth of all test fungi in this work.

Table 2. Antifungal activity of compounds against fungus *F. proliferatum*, test dosage (mg/ml)

	1	0.5	0.25	0.125	0.0625
Compounds	% mycelial inhibition				
1	84	68	60	40	24
2	16	12	-	-	-
3	20	8	8	-	-
5	4	4	-	-	-
6	16	16	16	16	12
8	12	12	-	-	-
9	12	8	8	8	-
10	40	32	32	16	12

(-) indicates no inhibition of mycelial growth

Table 3. Antifungal activity of compounds against fungus *A. parasiticus* , test dosage (mg/ml)

	1	0.5	0.25	0.125	0.0625
Compounds	% mycelial inhibition				
1	79	75	42	21	-
2	13	4	-	-	-
3	4	4	-	-	-
5	4	-	-	-	-
6	4	-	-	-	-
8	4	4	-	-	-
10	29	25	25	17	13

(-) indicates no inhibition of mycelial growth

Table 4. Antifungal activity of compounds against fungus *A. niger*, test dosage (mg/ml)

	1	0.5	0.25	0.125	0.0625
Compounds	% mycelial inhibition				
1	65	41	-	-	-
3	6	6	-	-	-
8	6	6	6	-	-

(-) indicates no inhibition of mycelial growth

Table 5. Antifungal activity of compounds against fungus *T. reseii*, test dosage (mg/ml)

	1	0.5	0.25	0.125	0.0625
Compounds	% mycelial inhibition				
1	56	50	22	11	11
3	6	-	-	-	-
7	11	11	11		-
10	39	17	17	-	-

(-) indicates no inhibition of mycelial growth

3. Experimental

^{1}H NMR spectra were recorded on Varian Mercury 400 NMR spectrometer, unless otherwise stated. Chemical shifts are reported as δ in units of parts per million (ppm) relative to tetramethylsilane (δ 0.00 singlet) in deuterated chloroform ($CDCl_3$). ^{13}C NMR spectra were recorded

on Varian Mercury 400 (100 MHz). Melting points were obtained on an Electrothermal 9100 capillary melting point apparatus and are uncorrected. Infrared spectra (IR) of all compounds were recorded in dichloromethane (CH_2Cl_2) using a Mattson 1000 FTIR Spectrophotometer. Microanalyses for C, H, N was performed Leco 932 Elemental Analyzer (CHNS-O). All reactants were reagent grade and were used as received.

3.1.General Procedure for Synthesis of Schiff Bases: The synthesis of 3-Amino-2-isopropyl-3H-quinazolin-4-one **1** were in 42% overall yield in two steps, according to the procedure of Barker[46], starting from methylanthranilate and isobutyric anhydride and the final adduct **1** checked by the NMR spectrum: 1H NMR (200 MHz) ($CDCl_3$): 8.15 (1H, d, 7.7 Hz, 5-*H* (Q)), 7.61-7.68 (2H, m, 7-*H* and 8-*H* (Q)), 7.36 (1H, ddd, 9.53 Hz, 8.06 Hz and 1.46 Hz 6-*H* (Q)), 4.87 (2H, s, NH_2), 3.72 (1H, heptet, *J* 6.9 CH_3CHCH_3) and 1.33 (6H, d, 6.6 Hz, CH_3CHCH_3) (mp 100-102 ^oC, lit.[46] 80 ^oC). The starting 3-aminoquinazolinone **1** (1 mol eq) was dissolved in glacial acetic acid and appropriate aldehydes (3 to 4eq), then, solution was refluxed at 120 ^oC and reactions were finished by controlling TLC. Water is added and extracted by CH_2Cl_2 (3x20 cm^3) and organic phase evaporated then $NaHSO_3$ solution (33%) added and stirred for 15 min to remove excess aldehydes. To the resulting material CH_2Cl_2 added (20 cm^3) and washed with saturated aqueous sodium hydrogen carbonate solution (30 cm^3). The organic layer was separated, dried with sodium sulphate and the solvent removed by evaporation under reduced pressure. The crude product crystallised on addition of ethanol.

3.2.1. 3-(Benzylidene-amino)-2-isopropyl-3H-quinazolin-4-one 2: Yield 77%, mp 129-131 ^oC (lit. 145 ^oC)[46] (from ethanol). IR (in CH_2Cl_2 solution) $\nu_{max/}$ cm^{-1}: 3064w, 2971m, 2933w 1676s, 1611s, 1594s, and 1568m. ^1H NMR: δ 8.98 (1H, s, NC*H*), 8.28 (1H, dd, *J* 8.29 Hz, and 1.1 Hz, 5-*H* (Q)), 7.91 (2H, dd, *J* 8.1 Hz, and 1.5 Hz, (Ph*H*-o)), 7.72 (2H, m, 7-H and 8-*H* (Q)), 7.57-7.42 (4H, m, (Ph*H*) and 6-*H* (Q)), 3.56 (1H, heptet, *J* 6.6 Hz, CH_3CH CH_3) and 1.37 (6H, d, *J* 6.59 Hz, CH_3CHCH_3). ^{13}C NMR: δ 167.2, 160.6, 159.1, 146.8, 134.3, 133.1, 132.6, 129.2, 129.1, 127.6, 127.3, 126.5, 121.6, 32.1 and 20.6). Elemental analysis calculated for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42%. Found: C, 74.44; H, 5.83; N, 14.42%.

3.2.2. 2-Isopropyl-3-[(2-methoxy-benzylidene)-amino]-3H-quinazolin-4-one 3: Yield 82%, mp 116-118 ^oC (from ethanol). IR (in CH_2Cl_2 solution) $\nu_{max/}$ cm^{-1}: 3067w, 2971m, 2934w 2872w, 2835w, 1677s, 1613m, 1594s, and 1579m. ^1H NMR: δ 8.92 (1H, s, NC*H*), 8.27 (1H, ddd, *J* 8.06 Hz, 2.1 Hz and 1.1 Hz, 5-*H* (Q)), 7.75-7.09 (7H, m, (Ar*H*), 6-*H*, 7-*H* and 8-*H* (Q)), 3.87 (3H, s, OCH_3), 3.54 (1H, heptet, *J* 6.96 Hz, CH_3CH CH_3), and 1.35 (6H, d, *J* 6.96 Hz, CH_3CHCH_3). ^{13}C NMR: δ 167.3, 160.5, 160.1, 159.0, 146.8, 134.3, 130.2, 127.6, 127.4, 126.5, 126.4, 122.2, 121.5, 119.1, 112.6, 55.6, 32.0 and 20.6). Elemental analysis calculated for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08%. Found: C, 71.06; H, 6.18; N, 12.97%.

3.2.3. 3-[(2-Chloro-benzylidene)-amino]-2-isopropyl-3H-quinazolin-4-one 4: Yield 68%, mp 121-123 ^oC (from ethanol). IR (in CH_2Cl_2 solution) $\nu_{max/}$ cm^{-1}:, 3069w, 2974m, 2933w 2873w, 2610w, 1682s, 1608s, 1593s, and 1568w. ^1H NMR: δ 9.48 (1H, s, NC*H*), 8.31 (1H, dd, *J* 7.33 Hz and 1.46 Hz, Ar*H*-o), 8.26 (1H, dd, *J* 7.69 Hz and 1.46 Hz, 5-*H* (Q)), 7.76-7.25 (6H, m, (Ar*H*), 7-H and 8-*H* (Q)), 3.54 (1H, heptet, *J* 6.96 Hz, CH_3CH CH_3), and 1.37 (6H, d, *J* 6.59 Hz, CH_3CHCH_3). ^{13}C NMR: δ 163.8, 160.5, 159.0, 146.7, 136.5, 134.4, 133.4, 130.9, 130.4, 128.3, 127.6, 127.5, 127.4, 126.5, 121.6, 32.1 and 20.6). Elemental analysis calculated for $C_{18}H_{16}ClN_3O$: C, 66.36; H, 4.95; N, 12.90%. Found: C, 66.62; H, 4.77; N, 12.85%.

3.2.4. 3-[(4-Dimethylamino-benzylidene)-amino]-2-isopropyl-3H-quinazolin-4-one 5: Yield 69%, mp 203-205 ^oC (from ethanol). IR (in CH_2Cl_2 solution) $\nu_{max/}$ cm^{-1}: 3320w, 2967w, 2934w, 2872w, 2820w, 1667s, 1617w, 1591s, and 1562m. ^1H NMR: δ 8.58 (1H, s, NC*H*), 8.28 (1H, ddd, *J* 7.69 Hz,1.83 Hz and 1.1 Hz 5-*H* (Q)), 7.78 (2H, dd, *J* 6.96 Hz and 2.1 Hz, (Ph-o)), 7.70 (2H, m, 7-H and 8-*H* (Q)), 7.42 (1H, m, 6-*H* (Q)), 6.73 (2H, d, *J* 8.79 Hz, (Ar*H*)), 3.54 (1H, heptet, *J* 6.96 Hz, CH_3CH CH_3), 3.06 (6H, s, $(CH_3)_2N$ and 1.34 (6H, d, *J* 6.96 Hz, CH_3CHCH_3). ^{13}C NMR: δ 168.4, 160.8, 159.2, 153.4, 147.0,

133.9, 130.9, 127.5, 127.2, 126.2, 121.6, 120.1, 111.7, 40.3, 31.8 and 20.5). Elemental analysis calculated for $C_{20}H_{22}N_4O$: C, 71.83; H, 6.63; N, 16.75%. Found: C, 72.15; H, 6.77; N, 16.44%.

3.2.5. 3-[(2-Hydroxy-benzylidene)-amino]-2-isopropyl-3H-quinazolin-4-one 6: Yield 71%, mp 128-130 ^oC (from ethanol). IR (in CH_2Cl_2 solution) $\nu_{max/}$ cm^{-1}:, 3157m, 2975m, 2934w, 2873w, 1680s, 1621s, 1596s, and 1568w. ^1H NMR: δ 10.84 (1H, s, ArO*H*), 8.90 (1H, s, NC*H*), 8.23 (1H, dd, *J* 7.69 Hz and 1.1 Hz, 5-*H* (Q)), 7.73-6.94 (7H, m, (Ar*H*), 6-*H*, 7-*H* and 8-*H* (Q)), 3.37 (1H, heptet, *J* 6.59 Hz, CH_3CH CH_3), and 1.35 (6H, d, *J* 6.59 Hz, CH_3CHCH_3). ^{13}C NMR: δ 172.0, 160.3, 159.2, 158.7, 146.7, 134.8, 134.6, 133.7, 127.7, 127.4, 126.8, 121.3, 120.1, 117.7, 116.6, 32.1 and 20.6). Elemental analysis calculated for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67%. Found: C, 70.24; H, 5.77; N, 13.59%.

3.2.6. 2-Isopropyl-3-[(4-methyl-benzylidene)-amino]-3H-quinazolin-4-one 7: Yield 82%, mp 134-135 ^oC (from ethanol). IR (in CH_2Cl_2 solution) $\nu_{max/}$ cm^{-1}:, 28671m, 1672s, 1592s, and 1570s. ^1H NMR: δ 8.89 (1H, s, NC*H*), 8.27 (1H, d, *J* 8.06 Hz, 5-*H* (Q)), 7.80 (2H, d, *J* 8.06 Hz, (Ar*H*-o)), 7.71 (2H, d, *J* 3.29 Hz, 7-H and 8-*H* (Q)), 7.42 (1H, m, 6-*H* (Q)), 7.29 (2H, d, *J* 7.69 Hz, 5-*H* (Q)), 3.55 (1H, heptet, *J* 6.96 Hz, CH_3CH CH_3), 2.42 (3H, s, CH_3Ph and 1.36 (6H, d, *J* 6.59 Hz, CH_3CHCH_3). ^{13}C NMR: δ 167.5, 160.6, 159.1, 146.8, 143.4, 134.2, 130.3, 129.9, 129.1, 127.6, 127.3, 126.4, 121.6, 32.1, 21.9 and 20.6). Elemental analysis calculated for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76%. Found: C, 74.90; H, 6.36; N, 13.78%.

3.2.7. 2-Isopropyl-3-(3-phenyl-allylideneamino)-3H-quinazolin-4-one 8: Yield 66%, mp 135-136 ^oC (from ethanol). IR (in CH_2Cl_2 solution) $\nu_{max/}$ cm^{-1}:, 3062w, 3027w, 2972m, 2932w, 1675s, 1627m, 1595s, and 1565w. ^1H NMR: δ 8.64 (1H, d, *J* 8.06 Hz, NC*H*), 8.26 (1H, d, *J* 7.69 Hz, 5-*H* (Q)), 7.73-7.11 (10H, m, (Ar*H*), 6-*H*, 7-*H*, 8-*H* (Q) and CHC*H*=C*H*Ar), 3.51 (1H, heptet, *J* 6.96 Hz, CH_3CH CH_3), and 1.35 (6H, d, *J* 6.96 Hz, CH_3CHCH_3). ^{13}C NMR: δ 169.7, 160.4, 158.9, 146.8, 146.4, 135.3, 134.2, 130.3, 129.2, 128.0, 127.6, 127.3, 126.5, 126.4, 124.2, 121.5, 31.8 and 20.6). Elemental analysis calculated for $C_{20}H_{19}N_3O_2$: C, 75.69; H, 6.03; N, 13.24%. Found: C, 76.15; H, 6.02; N, 13.29%.

3.2.8. 3-[(Furan-2-ylmethylene)-amino]-2-isopropyl-3H-quinazolin-4-one 9: Yield 44%, mp 114-116 ^oC (from ethanol). IR (in CH_2Cl_2 solution) $\nu_{max/}$ cm^{-1}: 3119w, 3092w, 2986w, 2929w, 1673s, 1609s, and 1554w. ^1H NMR: δ 8.78 (1H, s, NC*H*), 8.22 (1H, d, *J* 7.69 Hz, 5-*H* (Q)), 7.71-7.25 (4H, m, (Furan*H*), 6-*H*, 7-*H* and 8-*H* (Q)), 7.03 (1H, d, *J* 3.3 Hz, Furan-H), 6.57 (1H, dd, *J* 3.3 Hz and 1.46 Hz, Furan-H), 3.57 (1H, heptet, *J* 6.96 Hz, CH_3CH CH_3), and 1.32 (6H, d, *J* 6.96 Hz, CH_3CHCH_3). ^{13}C NMR: δ 160.6, 159.0, 155.3, 148.4, 147.0, 146.7, 134.3, 127.5, 127.3, 126.5, 121.4, 118.7, 112.7, 31.9 and 20.6). Elemental analysis calculated for $C_{16}H_{15}N_3O_2$: C, 68.32; H, 5.27; N, 14.96%. Found: C, 68.13; H, 5.37; N, 14.71%.

3.2.9. 3-But-2-enylideneamino-2-isopropyl-3H-quinazolin-4-one 10: Yield 50%, mp 103-104 ^oC (from ethanol). IR (in CH_2Cl_2 solution) $\nu_{max/}$ cm^{-1}:, 3552w, 3066w, 2971m, 2933w, 2872w, 1678s, 1649m, 1598s, and 1568m. ^1H NMR: δ 8.35 (1H, d, J 8.79 Hz, NC*H*), 8.22 (1H, d, *J* 8.06 Hz, 5-*H* (Q)), 7.70-7.37 (3H, m, 6-*H*, 7-*H* and 8-*H* (Q)), 6.49 (2H, m, C*H*C*H*CH_3), 3.41 (1H, heptet, *J* 6.96 Hz, CH_3CH CH_3), 1.92 (3H, d, *J* 5.1 Hz, $CHCHCH_3$) and 1.28 (6H, d, *J* 6.96 Hz, CH_3CHCH_3). ^{13}C NMR: δ 170.3, 160.3, 158.8, 146.9, 146.7, 134.1, 128.3, 127.5, 127.2, 126.3, 121.5, 31.6, 20.5 and 19.2). Elemental analysis calculated for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46%. Found: C, 70.51; H, 6.67; N, 16.33%.

4. Conclusion

In conclusion, we conveniently condensed 3-aminoquinazolinone **1** with a series of aldehydes in the presence of acetic acid as solvent for preparing imines and evaluate their antifungal activities. In all cases, quinazolinone itself revealed significant fungiostatic activity against all filamentous fungi

tested. It is possible that combination of quinazolinone and lactam ring brings about synergistic effects on biological activities. Therefore lactamisation of imines under different conditions are underway in our laboratory.

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