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Design, synthesis and antibacterial evaluation of 2-alkyl- and 2-aryl-3-(phenylamino)quinazolin-4(3*H*)-one derivatives

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Abstract: 2-Alkyl and 2-aryl-3-(phenylamino)quinazolin-4(3*H*)-ones **4a–h** were synthesized in a one-pot three-component condensation of an isatoic anhydride **1a–h**, ethyl or methyl ortho ester and phenylhydrazine in the presence of $KAl(SO_4)_2 \cdot 12H_2O$ (alum) as a nontoxic, reusable, inexpensive and easily available catalyst. The synthesis was conducted under microwave irradiation or classical heating. Products **4a** and **4b** show good antimicrobial activities.

Keywords: alum; antimicrobial activity; isatoic anhydride; ortho esters; quinazolin-4(3*H*)-one.

Introduction

Quinazolin-4(3*H*)-one and its derivatives possess a wide spectrum of biological properties [1, 2], such as anti-inflammatory [3], antihypertensive [4], anti-HIV [5], anticancer [6], antiviral [7] and antibacterial activity [8]. In addition, these structural fragments are present in several bioactive natural products [9–11], such as *l*-vasicinone [12], chrysogine [13] and drugs [14] such as methaqualone [15], febrifugine and isofebrifugine [16, 17]. There are several methods in the literature for the preparation of quinazolin-4(3*H*)-ones [18–21]. These are cyclocondensation of 2-aminobenzamides with acyclic or cyclic 1,3-diketones catalyzed by $FeCl_3$ [22], condensation of 2-halobenzamides (or 2-halonicotinamides), aldehydes and sodium azide catalyzed by copper [23], reaction of benzoxazinones with primary aliphatic and aromatic amines [24], reaction of 2-iodoanilines with trimethyl orthoformate and amines in the presence of palladium on activated charcoal (Pd/C) [25] and condensation of anthranilic acid with acyl chlorides and aromatic/aliphatic amines in acidic ionic liquids under microwave irradiation [26].

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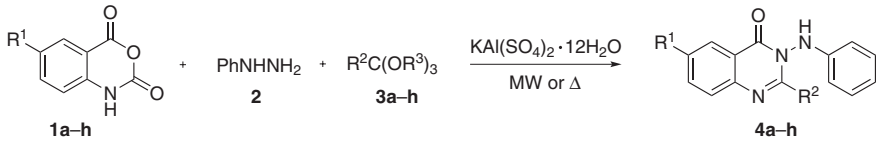
Results and discussion

Multicomponent reactions (MCRs) are powerful tools in the modern drug discovery process in terms of lead finding and lead optimization. Recently, we have reported the preparation of indenopyridine [27], bis[spiro(quinazoline-oxindole)] [28], bis-dihydroquinazolinone [29], 1′*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-dione [30] and 2-aryl-3-(phenylamino)-2,3-dihydroquinazolin-4(1*H*)-one [31] via multicomponent reactions. Along this line, we have designed a three-component one-step synthesis of quinazolin-4(3*H*)-ones. The use of $KAl(SO_4)_2 \cdot 12H_2O$ (alum), which is relatively nontoxic and inexpensive, is the center of our study [32, 33].

The reaction of isatoic anhydride **1a**, phenylhydrazine **2** and triethyl orthoformate **3a** in ethanol in the presence of a catalytic amount of alum under reflux conditions was completed in 130 min. Workup of the mixture furnished 3-(phenylamino)quinazolin-4(3*H*)-one (**4a**) in an 89% yield (Scheme 1). Encouraged by this success, we extended this reaction of phenylhydrazine **2** with a range of isatoic anhydrides **1b–h** and orthoesters **3b**–**h** under similar conditions, furnishing the respective 3-(phenylamino)quinazolin-4(3*H*)-one **4b–h** in good yields (Scheme 1). We then examined this reaction under microwave irradiation and found that it furnishes 3-(phenylamino)quinazolin-4(3*H*)-ones **4a–h** in a much shorter time of 5 min. In order to increase the energy input and provide a uniform heating, a small amount of *N*,*N*-dimethylacetamide (DMAC), an excellent energy-transfer solvent with a high dielectric constant, was added to the reaction mixture. The structures of all products were fully consistent with IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis data.

The synthesized compounds were screened *in vitro* for their antibacterial activities against Gram-negative



a: R^1 = H; R^2 = H; R^3 = Et; heating time: 130 min
b: R^1 = H; R^2 = Me; R^3 = Et; heating time: 140 min
c: R^1 = H; R^2 = Et; R^3 = Et; heating time: 150 min
d: R^1 = H; R^2 = ^{n}Pr; R^3 = Me; heating time: 160 min
e: R^1 = H; R^2 = ^{n}Bu; R^3 = Me; heating time: 180 min
f: R^1 = H; R^2 = Ph; R^3 = Me; heating time: 160 min
g: R^1 = Cl; R^2 = Me; R^3 = Et; heating time: 160 min
h: R^1 = Cl; R^2 = Et; R^3 = Me; heating time: 170 min

Scheme 1 Synthesis of 3-(phenylamino)quinazolin-4(3*H*)-ones **4a–h**.

bacteria *Escherichia coli*, ATCC 25922, *Pseudomonas aeruginosa*, ATCC 85327, *Klebsiella pneumonia*, ATCC 29655 and Gram-positive bacteria *Enterococcus faecalis*, ATCC 29737, *Bacillus subtilis* ATCC 465, *Bacillus pumilus* PTCC 1114, *Micrococcus luteus* PTCC 1110, *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228 and *Streptococcus mutans*, PTCC 1601. Inhibition zones (IZ) were measured by the disk diffusion method [34] and, subsequently, the minimum inhibitory concentrations (MIC) were also obtained [35].

Activities of the compounds were compared with those of tetracycline and gentamicin used as standards. The screening results indicate that some of the tested compounds exhibit significant antibacterial activities. Compound **4a**, unsubstituted at position 2 of the quinazoline moiety shows much better activity than the reference drugs. 2-Alkylquinazolines **4b–d** exhibit good activity, while the remaining compounds generally show inferior activities against the tested bacterial strains.

Conclusions

This paper describes a convenient and efficient method for the synthesis of 2-alkyl and 2-aryl-3-(phenylamino) quinazolin-4(3*H*)-one derivatives through the three-component reaction of an isatoic anhydride, an ortho ester and phenylhydrazine using $KAl(SO_4)_2 \cdot 12H_2O$ (alum) as a heterogeneous catalyst. The method offers a high yield of products and an easy work-up and uses an inexpensive, non-toxic and easily available catalyst.

Experimental

Melting points were obtained in open capillary tubes on an Electrothermal 9200 apparatus. Electron-impact mass spectra were recorded at 70 eV on a Shimadzu QP 1100BX mass spectrometer. IR spectra were recorded in KBr pellets on a Shimadzu IR-470 spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were determined on a Bruker 300 DRX Avance instrument. Elemental analyses for C, H and N were performed using a Heraus CHN rapid analyzer.

General procedures for the synthesis of 2-alkyl- and 2-aryl-3-(phenylamino)quinazolin-4(3*H*)ones 4a–h

Classical heating A mixture of an isatoic anhydride (**1**, 1 mmol), phenylhydrazine (**2**, 2 mmol), an ortho ester (**3**, 2 mmol), alum (0.15 g) and EtOH (10 mL) was stirred and heated under reflux for a period of time indicated in Scheme 1. After completion of the reaction (monitored by TLC, ethyl acetate/*n*-hexane, 1/1), the mixture was concentrated under reduced pressure and the residue was treated with water (20 mL). The resultant solid was separated by filtration and crystallized from ethanol.

Microwave irradiation A mixture of an isatoic anhydride (**1**, 1 mmol), phenylhydrazine (**2**, 1 mmol), an ortho ester **3** (2 mmol), alum (0.15 g) and five drops of *N,N*-dimethylacetamide (DMAC) was mixed thoroughly in a Pyrex test tube. The homogenized mixture was irradiated in a microwave oven in two stages, with a cooling period between the irradiations: 210 W for 3 min, cooling, then 360 W for 5 min. After cooling to room temperature, the mixture was treated with water (10 mL) and the resultant precipitate was filtered and crystallized from ethanol.

3-(Phenylamino)quinazolin-4(3*H*)-one(4a) This compound was obtained in yields of 89% (heat) and 93% (MW) as a white powder; mp 164–166°C; (lit. [36]: mp 166–167°C, yield 59%).

2-Methyl-3-(phenylamino)quinazolin-4(3*H*)-one (4b) This compound was obtained in yields of 90% (heat) and 95% (MW) as a white powder; mp 209–211°C; IR (ν/cm^{-1}): 3296, 1634, 1602(C=O); ^{1}H NMR (DMSO-d_6) δ 3.39 (s, 3H, CH_3), 6.65 (d, J=7.7 Hz, 2H, Ar), 6.83 (t, J=7.3 Hz, 1H, Ar), 7.19 (t, J=7.9 Hz, 2H, Ar), 7.50 (t, J=7.1 Hz, 1H, Ar), 7.67 (d, J=8.0 Hz, 1H, Ar), 7.84 (t, J=8.0 Hz, 1H, Ar), 8.09 (d, J=7.2 Hz, 1H, Ar), 9.13 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 21.8, 112.8, 120.7, 121.5, 126.6, 126.9, 127.3, 129.6, 135.1, 147.22, 147.29, 158.1, 160.6; MS: *m/z* 251 (M^+). Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.59; H, 5.11; N, 16.61.

2-Ethyl-3-(phenylamino)quinazolin-4(3*H*)-one (4c) This compound was obtained in 85% (heat) and 91% (MW) yields as a white powder; mp 163–165°C; IR (ν/cm^{-1}): 3264, 1640, 1608(C=O); ^{1}H NMR (DMSO-*d6*): δ 1.24 (t, *J*=7.5 Hz, 3H, CH_3), 2.63–2.76 (m, 1H, CH), 2.89–2.99 (m, 1H, CH), 6.61(d, *J*=7.9 Hz, 2H, Ar), 6.82 (t, *J*=7.5 Hz, 1H, Ar), 7.18 (t, *J*=7.5 Hz, 2H, Ar), 7.50 (t, *J*=7.5 Hz, 1H, Ar), 7.69 (d, *J*=7.9 Hz, 1H, Ar), 7.83 (t, *J*=7.5 Hz, 1H, Ar), 8.06 (d, *J*=7.9 Hz, 1H, Ar), 9.12 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 11.4, 27.1, 39.0, 112.8, 120.6, 121.4, 126.6, 126.9, 127.6, 129.6, 135.1, 147.1, 147.4, 160.6, 161.3; MS: *m/z* 265 (M$^+$). Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.33; H, 5.58; N, 15.73.

3-(Phenylamino)-2-propylquinazolin-4(3*H*)-one (4d) This compound was obtained in yields of 86% (heat) and 90% (MW) as a white powder; mp 160–162°C; IR (ν/cm^{-1}): 3311, 1648, 1607(C=O); ^{1}H NMR (DMSO-d_6): δ 0.93 (t, *J*=7.3 Hz, 3H, CH_3), 1.72–1.82 (m, 2H, CH_2), 2.61–2.71 (m, 1H, CH), 2.86–2.95 (m, 1H, CH), 6.61 (d, *J*=7.5 Hz, 2H, Ar), 6.82 (t, *J*=75 Hz, 1H, Ar), 7.18 (t, *J*=7.5 Hz, 2H, Ar), 7.50 (t, *J*=7.5 Hz, 1H, Ar), 7.69 (d, *J*=7.9 Hz, 1H, Ar), 7.84 (t, *J*=7.9 Hz, 1H, Ar), 8.06 (d, *J*=7.9 Hz, 1H, Ar), 9.11 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 14.1, 20.1, 35.63, 112.8, 120.6, 121.5, 126.6, 126.9, 127.6, 129.6, 135.1, 147.1, 147.5, 160.3, 160.7; MS: *m/z* 279 (M$^+$). Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 73.01; H, 6.01; N, 14.93.

2-Butyl-3-(phenylamino)quinazolin-4(3*H*)-one (4e) This compound was obtained in yields of 82% (heat) and 88% (MW) as a white powder; mp 172–174°C; IR (ν/cm^{-1}): 3296, 1626, 1604(C=O); ^{1}H NMR (DMSO-d_6): δ 0.91(t, *J*=7.5 Hz, 3H, CH_3), 1.28–1.40 (m, 2H, CH_2), 1.69–1.77 (m, 2H, CH_2), 2.49 (m, 1H, CH), 2.71(m, 1H, CH), 6.61 (d, *J*=8.4 Hz, 2H, Ar), 6.82 (t, *J*=7.5 Hz, 1H, Ar), 7.20 (t, *J*=7.5 Hz, 2H, Ar), 7.49 (t, *J*=7.5 Hz, 1H, Ar), 7.68(d, *J*=8.0 Hz, 1H, Ar), 7.83 (t, *J*=8.0 Hz, 1H, Ar), 8.06 (d, *J*=7.9 Hz, 1H, Ar), 9.11 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 14.1, 22.2, 28.8, 33.4, 112.8, 120.6, 121.5, 126.6, 126.9, 127.6, 129.6, 135.1, 147.1, 147.5, 160.6, 160.7; MS: *m/z* 293 (M$^+$). Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.58; H, 6.40; N, 14.20.

2-Phenyl-3-(phenylamino)quinazolin-4(3*H*)-one (4f) This compound was obtained in yields of 87% (heat) and 93% (MW) as a white powder; mp 185–187°C; IR (ν/cm^{-1}): 3253, 3028, 1675(C=O); ^{1}H NMR (DMSO-d_6): δ 6.57 (d, *J*=7.5 Hz, 2H, Ar), 6.75 (t, *J*=7.5 Hz, 1H, Ar), 7.11 (t, *J*=7.5 Hz, 2H, Ar), 7.38–7.44 (m, 3H, Ar), 7.58 (t, *J*=7.5 Hz, 1H, Ar), 7.73–7.81 (m, 3H, Ar), 7.91 (t, *J*=7.5 Hz, 1H, Ar), 8.13 (d, *J*=7.5 Hz, 1H, Ar), 9.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 112.8, 114.7, 115.07, 117.8, 119.7, 126.8, 128.0, 128.7, 129.3, 134.2, 141.2, 147.3, 148.3, 163.0, 164.7; MS: *m/z* 313 (M$^+$). Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.56; H, 4.70; N, 13.32.

6-Chloro-2-methyl-3-(phenylamino)quinazolin-4(3*H*)-one (4g) This compound was obtained in yields of 81% (heat) and 88% (MW) as a white powder; mp 197–198°C; (lit. [37]: mp 195–196°C, yield 64%).

6-Chloro-2-ethyl-3-(phenylamino)quinazolin-4(3*H*)-one (4h) This compound was obtained in yields of 80% (heat) and 90% (MW) yield as a white powder; mp 130–132°C; (lit. [37]: mp 131–131.5°C, yield 63%).

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