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A facile synthesis of novel unsymmetrical *N*-(4-oxo-2-phenyl-3(4*H*)-quinazolinoyl)-*N*-(aryl)acetamidines

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Abstract

A series of novel unsymmetrical *N*-(4-oxo-2-phenyl-3(4*H*)-quinazolinoyl)-*N*-(aryl)acetamidines was synthesized by reacting ethyl(1*E*)-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidoate (**2**) and suitable reactive aromatic amines. Structures' determination of the synthesized compounds was carried out using spectroscopic techniques including IR, ^{1}H NMR, and mass spectrometry. Structural effects on reactivity were also studied.

Keywords: 3-Amino-2-phenyl-4(3*H*)-quinazolinone; Triethylorthoacetate; Unsymmetrical *N*-(4-oxo-2-phenyl-3(4*H*)-quinazolinoyl)-*N*-(aryl)acetamidines

Amidine functionality finds its presence in many natural products and amidines are useful intermediates in the synthesis of many bioactive heterocyclic compounds [1,2]. Consequently, a plethora of methods have been reported for synthesis of amidines [3–8a,b]. Acetamidines and propinoamidines exhibit interesting biological activities such as anti-histamines, anti-hypertensive, anti-bacterial, anti-inflammatory, cardio-active, anti-diabetic, CNS depressant, antiprotozoal, anti-psychotic and anxiolytic [9–15]. Increasing interest in the chemistry of acetamidines is due to its ability to act as ligand for bridging metals, and also to produce chiral complexes [1].

Quinazolinones are cyclic amidine based heterocycles having significant role in synthetic chemistry. This class of compounds have drawn much attention because of their diverse biological activities such as hypnotic, sedative, analgesic, anticonvulsant, anti-tussive, anti-bacterial, anti-diabetic, anti-inflammatory, antitumor and HIV-1 reverse transcriptase inhibitor [16–23].

In recent years, the emphasis of drug design has focused on combination of pharmacophoric units resulting in chimerical molecules having more than one privileged structural moieties [24–26]. This prompted us to synthesize some new unsymmetrical quinazolin-4-one based acetamidines which are expected to prove as potential precursors for

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the synthesis of novel heterocyclic skeletons as well as pharmacologically lead compounds. Although the chemistry of quinazolin-4-ones is well explored however, to the best of our knowledge, the quinazolin-4-ones based acetamidines are being reported here for the first time.

1. Experimental

Chemicals and solvents used were of synthetic grade and further purified before use according to the standard methods. TLC analysis was done on aluminium supported pre-coated silica gel TLC plates (Merck). Melting points were determined in open capillary using Gallen kamp melting point apparatus. ^{1}H NMR spectra were recorded on Bruker 300 MHz and in $CDCl_3$, CD_3OD or DMSO-d_6 as solvent, using TMS as internal standard, while mass spectra were recorded on MAT312 instrument.

*1.1. Ethyl(1E)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)ethanimidoate (**2**)*

A mixture of 3-amino-2-phenyl-4(3*H*)-quinazolinone (0.2 g, 0.85 mmol), triethylorthoacetate (0.37 mL, 2.02 mmol) and 0.5 mL of glacial acetic were refluxed with continuous stirring for 5 h. After completion of reaction, the reaction mixture was poured into ice cold water, the product was separated as a white crystalline solid which was filtered, washed with water and recrystallized from ethanol to give **3** as white crystals; yield 83%. mp 132–133 °C; EI-MS *m/z*: 307 (M^+, 2), 279 (85), 237 (23), 202 (5), 105 (100), 77 (45), 51 (10); IR (KBr) υ_{max} (cm^{-1}): 3335 (2° N–H, str), 3233 (=C–H, str), 2868 (C–H, str), 1840 (C=C, overtone), 1720 (C=O, str), 1659 (C=C, str), 1431 (C–C–H, bend), 1217 (C–O, str), 1172; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (d, 1H, J = 8), 8.175 (d, 2H, J = 8), 7.92 (d, 1H, J = 7.8), 7.54 (m, 3H), 7.24 (m, 2H), 3.7 (q, 2H,), 2.65 (s, 3H), 1.24 (t, 3H).

*1.2. General procedure for the synthesis of acetamidines (**3–12**)*

Ethyl(1*E*)-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidoate (**2**) (0.2 g, 0.65 mmol) and suitable substituted aromatic amine (0.65 mmol) in equimolar ratio were fused to melt followed by adding glacial acetic acid (1–2 mL) and refluxed for 4-5 h. The completion of reaction was monitored by TLC. After completion the reaction mixture was evaporated under reduced pressure and the remaining mixture was allowed to cool to room temperature. The solid formed upon cooling was then treated with 0.8 mol/L HCl–MeOH and recrystallized from ethanol to yield the target amidines (**3**–**12**) in (46–95%) yield.

*1.2.1. N-(4-Oxo-2-phenyl-3(4H)-quinazolininyl)-N-(p-tolyl)acetamidine (**3**)*

Aromatic amine = *p*-toluidine (0.069 g, 0.65 mmol); yield (69%); mp 227–229 °C; IR (KBr) υ_{max} (cm^{-1}): 3233 (=C–H, str), 2868 (C–H, str), 1720 (C=O, str), 1659 (C=C, str), 1431 (C–C–H, bend), 1217 (C–O, str), 1172 (C–C, str), 813 (C–H, bend, arom), 765 (C–H, bend, arom), 685 (C–H, bend); MS (FAB, +ve, −ve) *m/z*: 369, 367; MS–EI (*m/z*); 368 (M^+, 35), 340 (7), 324 (4), 291 (73), 135 (3), 132 (14), 105 (100), 77 (81); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.9 (b, s, 1H, N–H), 8,47 (d, 1H, J = 7.8), 7.96 (m, 3H, Ar–H), 7.61 (m, 5H, Ar–H), 7.12 (q, 4H, Ar–H), 2.38 (s, 3H,), 2.16 (s, 3H).

*1.2.2. N-(4-Oxo-2-phenyl-3(4H)-quinazolininyl)-N-(p-bromophenyl)acetamidine (**4**)*

Aromatic amine = *p*-bromoaniline (0.112 g, 0.65 mmol); yield (90%); mp 244–246 °C; IR (KBr) υ_{max} (cm^{-1}): 3240 (N–H, str), 3078 (=C–H, str), 3005 (–C–H, str), 1668 (C=O, str), 1599 (C=C, str), 1424 (–C–H, bend), 1311 (C–H, str), 1258 (C=C, str), 1095 (bend), 881 (C–H, bend), 694 (–C–Br, str); EI-MS *m/z*: 434 (M+1, 11), 433 (10), 406 (3), 404 (3), 357 (18), 355 (18), 276 (2), 96 (3), 179 (6), 152 (1), 105 (100), 77 (89), 76 (9), 51 (13); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.92 (s, 1H, NH), 7.916 (d, 3H, J = 6.98), 7.77 (d, 2H, J = 8), 7.638–7.453 (m, 6H), 7.127–7.077 (t, 1H, J = 7.5), 7.0 (d, 1H, J = 7.64), 2.37 (s, 3H, CH_3).

*1.2.3. N-(4-Oxo-2-phenyl-3(4H)-quinazolininyl)-N-(phenyl)acetamidine (**5**)*

Aromatic amine = aniline (0.0605 g, 0.65 mmol); yield (57%); mp 233–236 °C; IR (KBr) υ_{max} (cm^{-1}): 3222 (N–H, str), 3078 (=C–H, str), 2992 (C–H, str), 1680 (C=O, str), 1614 (C=N, str), 1574 (C=C, str), 1424 (=C–H, bend), 1311 (=C–H, bend), 1258 (C–C, str), 881, 772, 752 (C–H, bend, arom); MS (FAB, +ve, −ve) *m/z*: (340, 338); EI-MS *m/z*:

354 (M^+, 81), 339 (12), 328 (39), 313 (12), 277 (86), 264 (27), 261 (41), 222 (89), 209 (18), 181 (55), 133 (31), 105 (100), 103 (16), 77 (83), 58 (12), 54 (14); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.05 (b, s, 1H, N–H), 8.09 (d, 1H, J = 8), 7.3 (d, 2H, J = 8), 7.88–7.83 (m, 4H), 7.76 (t, 1H, J = 8), 7.61–7.57 (m, 3H), 7.07 (d, 2H, J = 8), 6.97 (t, 1H, J = 8), 2.34 (s, 3H, CH_3).

*1.2.4. N-(4-Oxo-2-phenyl-3(4H)-quinazolininyl)-N-(3-bromophenyl)acetamidine (**6**)*

Aromatic amine = 3-bromoaniline (0.112 g, 0.65 mmol); yield (60%); mp 222–225 °C; IR (KBr) υ_{max} (cm^{-1}): 3301 (N–H, str), 3078 (=C–H, str), 2992 (C–H, str) 1680 (C=O, str) 1614 (C=N, str), 1579 (C=C, str) 1424 (=C–H, bend), 1258 (C–C, str), 1174 (C–C, str), 982, 846 (C–H, ben, arom), 752 (C–Br, str); EI-MS *m/z*: 434 (M+1, 11), 433 (10), 406 (3), 404 (3), 357 (18), 355 (18), 276 (2), 196 (3), 179 (6), 152 (1), 105 (100), 77 (89), 76 (9), 51 (13); ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.05 (b, s, 1H, N–H), 8.09 (d, 1H, J = 8), 7.93 (d, 2H, J = 8), 7.88 (s, 1H), 7.76 (d, 1H, J = 8), 7.61 (m, 6H), 7.07 (t, 1H, J = 8), 6.97 (d, 1H, J = 8), 2.34 (s, 3H, CH_3).

*1.2.5. N-(4-Oxo-2-phenyl-3(4H)-quinazolininyl)-N-(3-naphthyl)acetamidine (**7**)*

Aromatic amine = 2-naphthylamine (0.093 g, 0.65 mmol); yield (66%); mp 218–220 °C; IR (KBr) υ_{max} (cm^{-1}): 3241 (N–H, str), 2933 (C–H, str), 2866 (C–H, str), 1651 (C=O, str), 1520 (C=C, str), 1417 (C–H, bend), 1203 (C–C, str), 975, 885, 780 (C–H, bend, arom); EI-MS *m/z*: 404 (M^+, 23), 376 (8), 327 (42), 299 (4), 261 (2), 230 (2), 222 (71), 168 (12), 127 (22) 105 (100), 77 (70); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.53 (s, 1H, N–H), 7.95 (d, 1H, J = 8), 7.83 (t, 1H, J = 8.3), 7.78 (t, 2H, J = 8), 7.71 (d, 2H, J = 7.6), 7.65–7.61 (m, 6H), 7.43–7.39 (m, 2H), 7.27 (t, 1H, J = 8.3), 7.12 (d, 1H, J = 7.89), 2.35 (s, 3H).

*1.2.6. N-(4-Oxo-2-phenyl-3(4H)-quinazolininyl)-N-(4-methoxyphenyl)acetamidine (**8**)*

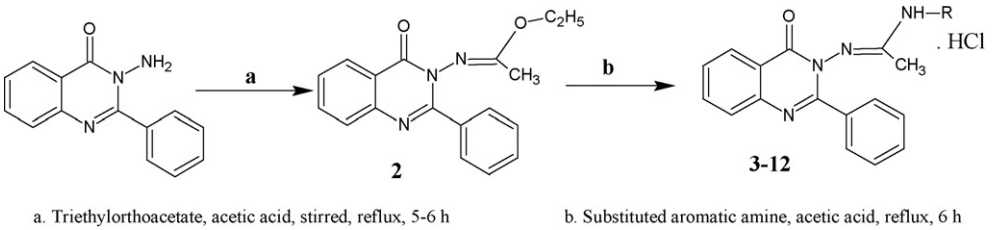
Aromatic amine = 4-anisidine (0.08 g, 0.65 mmol); yield (62%); mp 224–226 °C; IR (KBr) υ_{max} (cm^{-1}): 3312 (N–H, str), 3116 (=C–H, str), 2924 (C–H, str), 1167 (C=O, str), 1611 (C=C, str), 1586 (C=N, str), 1447 (=C–H, str), 1401 (=C–H, bend), 1322 (C–H, bend), 1304 (C–O, str), 1248 (C–C, str), 833, 745, 678 (C–H, bend, arom); EI-MS *m/z*: 384 (M^+, 36), 356 (6), 307 (49), 279 (2), 148 (9), 105 (100), 77 (74), 50 (10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.9 (b, s, 1H, N–H), 7.96 (m, 4H, Ar–H), 7.61 (m, 5H, Ar–H), 7.12 (m, 4H, Ar–H), 3.8 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3).

*1.2.7. N-(4-Oxo-2-phenyl-3(4H)-quinazolininyl)-N-(2,4,6-trimethoxyphenyl)acetamidine (**9**)*

Aromatic amine = 2,4,6-trimethylphenylamine (0.088 g, 0.65 mmol); yield (60%); mp 165–168 °C; IR (KBr) υ_{max} (cm^{-1}): 3241 (N–H, str), 2940 (=C–H, str), 1670 (C=O, str), 1630 (N=C, str), 1611 (C=C, str), 1447 (=C–H, bend), 1401 (C–H, bend), 1187 (C–C, str), 821, 745, 640 (C–H, bend, arom); EI-MS *m/z*: 396 (M^+, 2), 319 (2), 177 (40), 135 (100), 120 (54), 104 (15), 91 (28), 77 (24), 65 (12); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.01 (b, s, 1H), 8.14 (d, 1H, J = 8), 8.0–7.6 (m, 6H), 7.3 (d, 1H, J = 8), 6.93 (d, 1H, J = 8.34), 6.8 (s, 2H), 2.2 (s, 3H), 2.1 (s, 6H), 2.0 (s, 3H).

*1.2.8. N-(4-Oxo-2-phenyl-3(4H)-quinazolininyl)-N-(4-chlorophenyl)acetamidine (**10**)*

Aromatic amine = *p*-chlorophenylamine (0.166 g, 1.3 mmol); yield (80%); mp 252–255 °C; FAB-MS (+ve, −ve): 389, 387; EI-MS: 390 (M+1, 20), 388 (M^+, 54), 371 (6), 362 (5), 360 (59), 344 (6), 314 (27), 313 (27), 312 (17), 311 (87), 154 (4), 152c (11), 111 (8), 106 (8), 105 (100), 77 (44), 75 (4), 51 (5), 44 (8); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.36 (d, 1H, J = 8.3), 8.23 (d, 2H, J = 8.6), 8.02 (t, 1H, J = 9), 7.771 (d, 1H, J = 8.6), 7.68–7.63 (m, 1H), 7.39 (d, 1H, J = 9), 7.34 (t, 1H, J = 9), 7.15 (d, d, 2H, J = 8,3), 6.95 (d, 2H, J = 8.1), 2.23 (s, 3H, CH_3).



Scheme 1. General scheme for the synthesis of *N*-(4-oxo-2-phenyl-3(4*H*)-quinazolinoyl)-*N*-(aryl)acetamidines (**3**–**12**). (a) Triethylorthoacetate, acetic acid, stirred, reflux, 5–6 h and (b) substituted aromatic amine, acetic acid, reflux, 6 h.

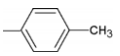
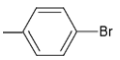
*1.2.9. N-(4-Oxo-2-phenyl-3(4H)-quinazolininyl)-N-(4-iodophenyl)acetamidine (**11**)*

Aromatic amine = *p*-iodophenylamine (0.284 g, 1.3 mmol); yield (81%); mp 248–250 °C; FAB-MS (+ve, −ve): (482, 479); IR (KBr) υ_{max} (cm^{-1}): 3222 (N–H, str), 3078 (C–H, str), 1921 (overtone), 1668 (C=O, str), 1614 (C=C, str), 1504 (C=N, str), 1424 (C–H, bend), 1174 (C–C, str), 982, 846, 752 (C–H, bend, arom); EI-MS *m*/*z*: 480 (M^+, 89), 479 (9), 463 (7), 453 (5), 452 (21), 436 (7), 404 (16), 403 (81), 354 (11), 278 (4), 277 (23), 276 (20), 233 (4), 179 (5), 106 (9), 105 (100), 77 (50), 76 (12), 51 (6); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.5 (b, s, 1H, NH), 8.43 (d, 1H, J = 8), 8.02–7.97 (m, 2H), 7.71–7.69 (m, 2H), 7.63–7.59 (m, 3H), 7.532–7.51 (m, 2H), 7.365 (t, 1H, J = 7.8), 7.15 (d, 2H, J = 8.1), 2.23 (s, 3H, CH_3).

*1.2.10. N-(4-Oxo-2-phenyl-3(4H)-quinazolininyl)-N-(4-hydroxyphenyl)acetamidine (**12**)*

Aromatic amine = *p*-hydroxyaniline (0.1068 g, 0.979 mmol); yield; 77%, mp 255–258 °C; FAB-MS (+ve, −ve): (371, 369); IR (KBr) υ_{max} (cm^{-1}): 3471 (O–H, str), 3251 (N–H, str), 2880 (C–H, str), 1664 (C=O, str), 1603 (C=N, str), 1540 (C=C, str), 1449 (C–H, bend), 1255 (C–C, str), 796, 757, 700 (C–H, bend, arom); EI-MS *m*/*z*: 370 (M^+, 8.59), 369 (14), 293 (34), 106 (12), 105 (100), 93 (5), 78 (9), 77 (87), 65 (13), 51 (10); ^{1}H NMR (300 MHz, $CDCl_3$): δ

Table 1
List of *N*-(4-oxo-2-phenyl-3(4*H*)-quinazolinoyl)-*N*-(aryl)acetamidines (**3**–**12**) synthesized.

No.	R
3	
4	
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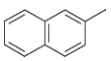
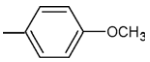
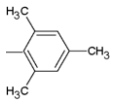
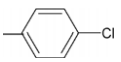
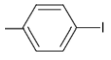
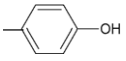
7	
8	
9	
10	
11	
12	

11.03 (b, s, 2H, NH), 7.92 (d, 1H, J = 9.6), 7.80 (d, 2H, J = 8.7), 7.767 (t, 1H, J = 8.6), 7.61 (d, 1H, J = 8.6), 7.58–7.53 (m, 1H), 7.748–7.35 (m, 3H), 7.29 (d, 2H, J = 7.9), 6.97 (d, 2H, J = 8.23), 2.01 (s, 3H, CH_3).

2. Results and discussion

2-Phenyl-3-amino-(4*H*)-3,1-benzoxazinone-4-one prepared according to our recently reported method [22], upon further reflux with triethylorthoacetate in glacial acetic acid gave ethyl(1*E*)-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidoate (**2**) *via* modification of the reported procedure [27]. Eventually the synthesis of a series of novel quinazolin-4(3*H*)-ones based acetamidines was accomplished by reacting compound **2** with selected aromatic amines (Scheme 1). Interesting electronic effects on the reactivity of aromatic amines with the imidate ester **2** were observed. Aromatic amines with electron-withdrawing groups failed to react with **2** while aromatic amines having electron-donating substituents reacted smoothly and gave the target compounds (**3**–**12**) in good yields (Table 1).

Similarly alkyl amines namely butylamine, propylamine, ethylenediamine, and benzylamine failed to react. This explanation is supported by the higher reactivity in case of aromatic amines having electron-donating substituents on benzene ring. Mass spectrometry, both EI and FAB along with ^{1}H NMR and IR were used for structure elucidation. Molecular ion peaks were confirmed from both FAB (+ve, −ve) mass data, while EI was used for the determination of the fragmentation pattern.

3. Conclusions

Ethyl(1*E*)-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidoate (**2**) gave the corresponding acetamidines in good yields on reaction with aromatic primary amines and amine having electron-donating groups, while failed to react with aromatic amines possessing electron-withdrawing groups. Alkylamines were also found to afford the desired products under the same reaction conditions. Thus the reaction is controlled by the nucleophilicity of the amines and the thermodynamic stabilization through tautomerism. The synthesized quinazolinylacetamidines are expected as biologically active new compounds and the potential activities are in the process of exploration.

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