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Synthesis, Characterization and Biological Activity of New 3(4*H*)-Quinazolinone Derivatives[1]

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Abstract—Quinazolinylbenzoic acid **1** was used as a precursor for synthesis of many heterocyclic systems. Ethyl 4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]benzoate **2** upon reaction with hydrazine hydrate gave 4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]benzoate benzoylhydrazide **3**. Compound **3** on treatment with 3-nitrobenzaldehyde, acetyl acetone, ethyl acetoacetate, and ammonium thiocyanate yielded compounds **4**–**8,** respectively. Isothiocyanate **8** was used for the synthesis of other quinazoline derivatives **9–16** via the reactions with various reagents. All newly synthesized quinazolinone derivatives have been characterized by ^{1}H NMR, IR, and mass spectroscopy. Most of the synthesized products were evaluated for their antibacterial and antifungal activities and some of those demonstrated high activity.

Keywords: quinazolinylbenzoic acid, isothiocyanate cyclization, antimicrobial activity
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4(3*H*)-Quinazolinone derivatives possess diverse biological and pharmacological activities [1–6] including antibacterial [7], antihypertensive [8], anticonvulsant [9], anti-allergic [10], and anticancer [11]. In continuation of our studies devoted to chemistry of quinazoline derivatives [12–17], we report here synthesis of new quinazoline derivatives bearing different heterocyclic moieties using quinazolinylbenzoic acid as the starting material. In the drug discovery process substituted oxazoles and their analogs have been used for the synthesis of various biologically active molecules and drugs [18–21].

EXPERIMENTAL

The chemical reagents were purchased from Sigma-Aldrich. TLC was carried out on pre-coated silica gel polyester sheets (kieselgel 60 F245, 0.02 mm, Merck). Melting points were measured uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 298 spectrophotometer. ^{1}H NMR spectra were measured on a Varian Gemini 200 MHz spectrometer in DMSO-d_6 using TMS as the internal reference. Mass spectra were measured on a Jeol JMS D-300 spectrometer operating at 70 eV. Micro-analysis was conducted on a 1106 Elemental Analyzer.

Ethyl 4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]benzoate (2). A mixture of **1** (0.01 mol) in absolute ethanol (40 mL) containing conc. H_2SO_4 (3 mL) was refluxed for 4 h, then concentrated, cooled down and poured onto ice. The solid residue crystallized from ethanol to give **2**. Yield 71%, mp 104–106°C. IR spectrum, ν, cm^{-1}: 3014 (CH aromatic), 2910 (CH aliphatic), 1739, 1681 (CO), 1610 (CN). ^{1}H NMR spectrum, δ, ppm: 1.3 t (3H, $CH_2\underline{CH_3}$), 4.30 q (2H, CH_2, ester), 7.30–8.01 m (13H, C_6H_5, C_6H_4). MS, *m/z* [*M*]$^+$: 370 (370.34). Found, %: C 74.53; H 4.82; N 7.54. $C_{23}H_{18}N_2O_3$. Calculated, %: C 74.59; H 4.86; N 7.57.

4-(2-Phenyl-oxo-4*H*-quinazolin-3-yl)benzoylhydrazide (3). A mixture of **2** (0.01 mol) with hydrazine hydrate (0.01 mol) was refluxed in ethanol (40 mL) for 3 h. The reaction mixture was poured onto ice-HCl and the solid product was filtered off and crystallized from ethanol to give **3.** Yield 68%, mp 126°C. IR spectrum, ν, cm^{-1}: 3475–3212 (NH, NH_2), 1691 (CO), 1610 (CN). ^{1}H NMR spectrum, δ, ppm: 2.00 s (2H, NH_2), 7.35–8.01 m (13H, C_6H_5, C_6H_4), 8.00 s (1H, $CONH_2$). MS, *m/z* [*M*]$^+$: 356 (356.21). Found, %: C 70.74; H 4.47; N 15.71. $C_{21}H_{16}N_4O_2$. $C_{21}H_{16}N_4O_2$. Calculated, %: C 70.79; H 4.49; N 15.73.

***N*-[3-Nitrobenzylidene]-4-[2-phenyl-4-oxo-quinazolin-3(4*H*)-yl]benzoylhydrazide (4).** A mixture of **3** (0.01 mol) with 3-nitrobenzaldehyde (0.01 mol) in

[1] The text was submitted by the author in English.

presence of piperidine (0.5 mL) was refluxed for 4 h. The solid formed upon cooling was filtered off and crystallized from ethanol to give **4**. Yield 63%, mp 178°C. IR spectrum, ν, cm^{-1}: 3447 (NH), 1696, 1660 (CO), 1590 (CN), 1442 (NO_2). ^1H NMR spectrum, δ, ppm: 7.40–7.90 m (17H, Ar-H), 9.92 s (1H, CH=N), 10.08 br (1H, NH). MS, *m/z* $[M]^+$: 490. Found, %: C 68.67; H 3.86; N 14.29. $C_{28}H_{19}N_5O_4$. Calculated, %: C 68.71; H 3.89; N 14.31.

3-[4-(3,5-Dimethyl-1*H*-pyrazole-1-carbonyl)phenyl]-2-phenylquinazolin-4(3*H*)-one (5). A mixture of acid hydrazide **3** (0.01 mol) with acetyl acetone (0.01 mol) in presence of few drops of acetic acid was refluxed for 4 h, then poured onto ice and filtrated. The residue was crystallized from ethanol to give **5**. Yield 59%, mp 60°C. IR spectrum, ν, cm^{-1}: 3436 (NH), 1710, 1657 (CO), 1605 (CN). ^1H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3, pyrazole), 2.48 s (3H, CH_3, pyrazole), 6.18 s (1H, olefinic of pyrazole),7.40–8.03 m (13H, Ar-H). MS, *m/z* $[M]^+$: 490 (490.34). Found, %: C 74.26; H 4.73; N 13.30. $C_{28}H_{19}N_5O_4$. Calculated, %: C 74.29; H 4.76; N 13.33.

3-[4-(3-Methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-1-carbonyl)phenyl]-2-phenylquina-zolin-4(3*H*)-one (6). A mixture of compound **3** (0.01 mol) with ethyl acetoacetate (0.01 mol) in presence of few drops of acetic acid was refluxed for 4 h, then poured onto ice. The residue was filtered off and crystallized from ethanol to give **6**. Yield 62%, mp 62°C. IR spectrum, ν, cm^{-1}: 1705, 1680, 1657 (CO), 1605 (CN). ^1H NMR spectrum, δ, ppm: 1.92 s (3H, CH_3, pyrazole), 2.20 s ($2H_2$, cyclic), 7.30–8.01 m (13H, Ar-H). MS, *m/z* $[M]^+$: 423 (423.17). Found, %: C 71.06, H 4.24 N 13.23. $C_{25}H_{18}N_4O_3$. Calculated, %: C 71.09, H 4.27, N 13.27.

2-Phenyl-3-[4-(5-thioxo-4,5-dihydro-1*H*[1,2,4]triazol-3-carbonyl]phenylquinazolin-3(4*H*)-one (7). A mixture of **3** (0.01 mol) with ammonium thiocyanate (0.01 mol) was fused in an oil-bath at above melting point of compound **3** for 30 min, then poured in cold water. The solid residue was crystallized from ethanol to give **7**. Yield 62%, mp 180°C. IR spectrum, ν, cm^{-1}: 3240-2330 (NH), 1710, 1665 (CO), 1605 (CN) 1237 (C=S). ^1H NMR spectrum, δ, ppm: 2.00 s (1H, NHC=S), 7.00 s (1H, NNHC=S), 7.3–8.01 m (13H, Ar-H). MS, *m/z* $[M]^+$: 426 (426.39). Found, %: C 64.92; H 3.52; N 16.45. $C_{23}H_{15}N_5O_2S$. Calculated, %: C 64.94; H 3.53; N 16.47.

4-(2-Phenyl-4-oxo-4*H*-quinazolin-3-yl)benzoylisothiocyanate (8). To a stirred solution of quinazolinylbenzoyl chloride (0.01 mol) in dry acetone (30 mL), solid ammonium thiocyanate (0.01 mol) was added. The reaction mixture was stirred for 1 h at room temperature. Ammonium chloride was precipitated in the course of the reaction and separated by filtration, leaving a clear solution of quinazolinyl isothiocyanate **8**.

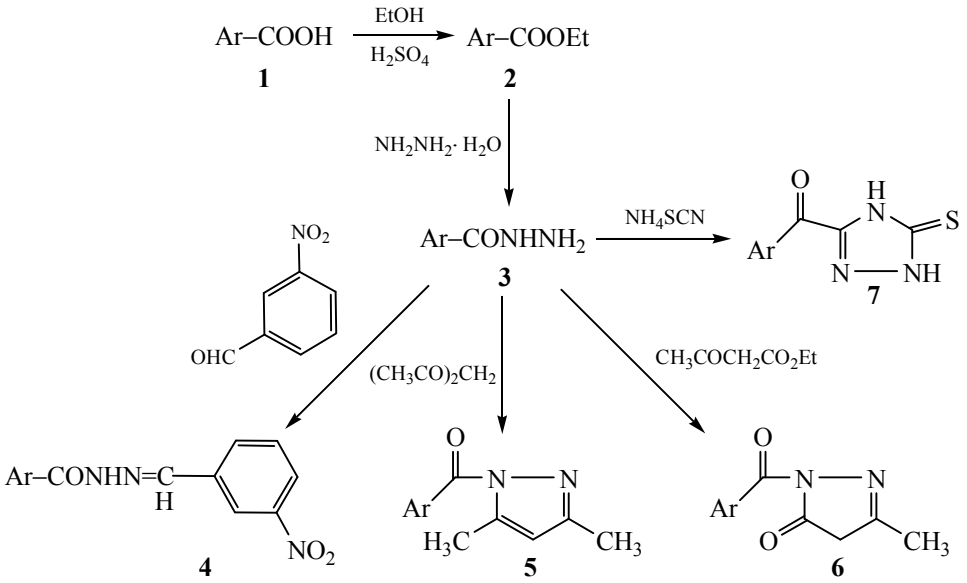
2-Phenyl-3-{4-(2-phenyl-5-thioxo)-2,4-dihydro-1*H*[1,2,4]triazolidin-3-yl}phenyl-quinazoline-4(3*H*)-one (9). A mixture of **8** (0.01 mol) with phenyl hydrazine (0.01 mol) was refluxed in dry acetone for 1 h. The reaction mixture, after cooling and concentration, was filtered and the residue was crystallized from benzene to give **9**. Yield 65%, mp 213°C. IR spectrum, ν, cm^{-1}: 3240–2330 (NH), 1690, 1655, 1645 (CO), 1605 (CN), 1257 (C=S). ^1H NMR spectrum, δ, ppm: 1.50 s (1H, SH), 2.00 s (1H, NH cyclic), 3.5-3.7 q (2H, CH_2, cyclic), 8.03 s (1H, NH), 7.35–8.03 m (13H, Ar-H). MS, *m/z* $[M]^+$: 474. Found, %: C 71.01; H 4.00; N 14.79; S 6.75. $C_{28}H_{19}N_5OS$. Calculated, %: C 71.04; H 4.02; N 14.80; S, 6.77.

***N*-(2-Mercapto-5-oxo-oxazolidin-2-yl)-4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]benzamide (10).** A mixture of **8** (0.01 mol) with glycine (0.01 mol) in pyridine was refluxed for 1 h. The reaction mixture was concentrated and upon cooling down it gave the solid product which was crystallized from acetic acid to give **10**. Yield 68%, mp 231°C. IR spectrum, ν, cm^{-1}: 3240–2330 (NH), 2160 (SH), 1690, 1655, 1645 (CO), 1605 (CN). ^1H NMR spectrum, δ, ppm: 1.50 s (1H, SH), 2.00 s (1H, NH, cyclic), 3.5–3.7 q (2H, CH_2, cyclic), 8.03 s (1H, CONH), 7.35–8.03 m (13H, Ar-H). MS, *m/z* $[M]^+$: 474 (474.51). Found, %: C 62.85; H 3.90; N 12.21; S 6.97. $C_{24}H_{18}N_4O_4S$. Calculated, %: C 62.88; H 3.93; N 12.23; S, 6.99.

2{3-[4-(2-Phenyl-4-oxo-4*H*-quinazolin-3-yl)benzoyl]thioureido}benzoic acid (11). A mixture of **8** (0.01 mol) with anthranilic acid (0.01 mol) was refluxed in dry acetone for 1 h. The reaction mixture was cooled down and the residue was crystallized from ethanol to give **11**. Yield 69%, mp 192°C. IR spectrum, ν, cm^{-1}: 3500–3150 (NH), 3400–2800 br (OH), 1690, 1655, 1645 (CO), 1605 (CN), 1254 (C=S). ^1H NMR spectrum, δ, ppm: 4.0 s (1H, CSNH), 8.00 s (1H, CONH), 7.35–8.03 s (17H, Ar-H), 11.03 s (1H, COOH). MS, *m/z* $[M]^+$: 521 (521.13). Found, %: C 66.90; H 3.83; N 10.75; S 6.13. $C_{29}H_{20}N_4O_4S$. Calculated, %: C 66.92; H 3.85; N 10.77; S 6.15.

2-Phenyl-3-[4-(4-oxo-5-thioxo)-1,4-dihydro-2*H*-quinazolin-3-carbonyl)-phenyl]-3*H*-quinazolin-4-

Scheme 1.



one (12). Compound **11** (1 g) was refluxed in acetic anhydride for 1 h. The reaction mixture was concentrated and the solid residue was crystallized from ethanol to give **12**. Yield 71%, mp 161°C. IR spectrum, ν, cm^{-1}: 3390 (NH), 1700 (CO), 1295 (C=S). MS, *m/z* $[M]^+$: 502 (502.33). Found, %: C 69.47; H 3.37; N 11.15; S, 6.36. $C_{29}H_{17}N_4O_3S$. Calculated, %: C 69.46; H 3.39; N 11.18; S, 6.39.

4-[(2-Phenyl-4-oxo-4*H*-quinazolin-3-yl)benzoyl]-thiocarbamic acid-*o*-(2-aminophen-yl) ester (13). A mixture of **8** (0.01 mol) with *o*-aminophenol (0.01 mol) in dry acetone was refluxed for 1 h. The reaction mixture was cooled down and the solid product was filtered off and crystallized from ethanol to give **13**. Yield 72%, mp 143°C. IR spectrum, ν, cm^{-1}: 3338 (NH), 1694 (CO), 1295 (C=S), 1100 (C–O). MS, *m/z* $[M]^+$: 492 (492.17). Found, %: C 68.41; H 3.85; N 11.40; S, 6.50. $C_{28}H_{19}N_4O_3S$. Calculated, %: C 68.43; H 3.87; N 11.41; S, 6.52.

***N*-Benzooxazol-2-yl-4-(2-phenyl-4-oxo-4*H*-quinazolin-3-yl)benzamide (14).** Compound **13** (1 g) was fused in a fusion tube for 1 h, then poured onto ice water and the solid residue was crystallized from acetic acid to give compound **14**. Yield 76%, mp 155°C. IR spectrum, ν, cm^{-1}: 3320 (NH), 1676 (C=O), 1587 (C=N).

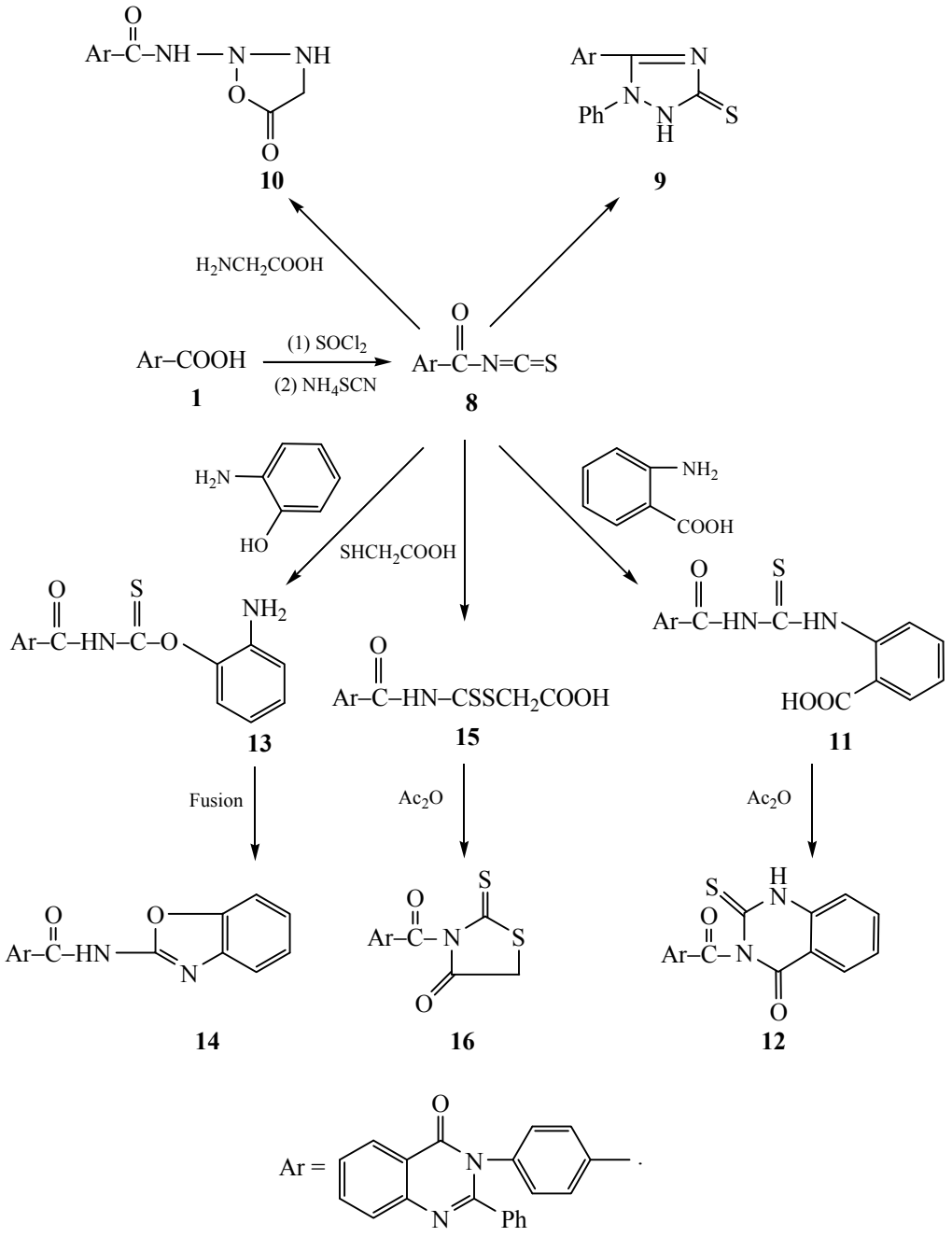
4-[(2-Phenyl-4-oxo-4*H*-quinazolin-3-yl)benzoyl-thiocarbamoylsulfanyl]acetic acid (15). A mixture of **8** (0.01 mol) with thioglycolic acid (0.01 mol) in dry acetone was refluxed for 1 h. The reaction mixture was cooled down and the solid product was crystallized from ethanol to give **15**. Yield 80%, mp 180°C. IR spectrum, ν, cm^{-1}: 3240–2330 (NH), 1710, 1665 (CO), 1690 (CO), 1605 (CN), 1237 (C=S). ^{1}H NMR spectrum, δ, ppm: 3.52 d (2H, CH_2), 7.00 s (1H, NNHC=S), 7.3–8.01 m (13H, Ar-H), 12.8 br (1H, COOH). MS, *m/z* $[M]^+$: 475 (475.36). Found, %: C 60.62; H 3.56; N 8.85; S, 13.45. $C_{24}H_{17}N_3O_4S_2$. Calculated, %: C 60.63; H 3.59; N 8.84; S, 13.47.

2-Phenyl-3-[4-(4-oxo-5-thioxothiazolidin-3-carbonyl)phenyl]-3*H*-quinazolin-4-one (16). Refluxing of compound **15** (1 g) in acetic anhydride for 2 h led to the product of cyclization. The solid residue was crystallized from ethanol to give **16**. Yield 79%, mp 138°C. IR spectrum, ν, cm^{-1}: 1705, 1680, 1657 (CO), 1605 (CN), 1299 (C=S). ^{1}H NMR spectrum, δ, ppm: 2.20 s ($2H_2$, cyclic), 7.30–8.01 m (13H, Ar-H). MS, *m/z* $[M]^+$: 446 (446.19). Found, %: C 62.00; H 3.35; N 9.40; S, 9.41. $C_{23}H_{15}N_3O_3S_2$. Calculated, %: C 62.02; H 3.37; N 9.44; S, 14.38.

RESULTS AND DISCUSSION

Our strategy was based on the use of readily available anthranilic acid and site-selective triple condensation reaction for the synthesis of 3(4*H*)-quinazolinone analogous. Esterification of compound **1** with absolute ethanol in presence of conc. H_2SO_4 gave ethyl 4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]benzoate **2**. Reaction of the ester **2** with hydrazine hydrate in

Scheme 2.



ethanol gave benzoylhydrazide **3**. The study of reactivity of benzoylhydrazide **3** towards aldehydes and active methylene compounds targeted preparation of biologically active pyrazole derivatives [22, 23]. Thus, the reaction of compound **3** with 3-nitrobenzaldehyde afforded *N*-(3-nitrobenzylidene)-4-[4-oxo-2-phenylquinazolin-3(4*H*)-benzoyl]hydrazide **4**. Reaction of compound **3** with acetyl acetone and/or ethyl acetoacetate afforded 3-[4-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)phenyl]-2-phenylquinazolin-4(3*H*)-one **5** and 3-[4-(3-methyl-4,5-dihydro-1*H*-pyrazole-3-carbonyl)phenyl]-2-phenylquinazolin-4(3*H*)-one **6**. Fusion of compound **3** with ammonium thiocyanate gave 2-phenyl-3-[4-(5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole-3-carbonyl)phenyl]quinazolin-4(3*H*)-one **7** (Scheme 1). Reaction of quinazolinylbenzoic acid **1** with thionyl chloride followed by treatment with ammonium thiocyanate in dry acetone [24] gave quina-

Antimicrobial activity of some synthesized compounds[a]

Comp. no.	*Bacillus Subtilis*	*Rhodococcus Equi*	*Salmonella typhimurium*	*Escherichia coli*	*Aspergillus Niger*	*Penicillium Notatum*
3	++	++	+++	++	–	–
4	++	+++	+++	+++	–	–
5	+++	+++	+++	+++	++	++
7	+++	+++	+++	++	++	++
9	+++	+++	+++	++	++	++
11	+++	+++	+++	++	++	++
15	+++	+++	+++	+++	++	++
14	+++	+++	++	++	++	++
16	+++	+++	++	+++	+	++
Amoxicillin	+++	+++	+++	+++	–	–
Sulphadiazine	–	–	–	–	+++	+++

[a] Inhibition zone diameter: (+++) (d > 12 mm, highly active), (++) (d = 9–12 mm, moderately active), (+) (d = 6–9 mm, slightly active), (−) (d < 6 mm, inactive).

zolinylisothiocyanate **8**, which was used as a building block for construction of biologically important triazole, oxazole and quinazoline derivatives. Thus, the reaction of compound **8** with phenyl hydrazine in dry acetone gave 2-phenyl-3-[4-(2-phenyl-5-thioxo-2,5-dihydro-1*H*-1,2,4-triazol-3-yl)phenyl]quinazolin-4(3*H*)-one **9** (Scheme 2). Reaction of **8** with glycine afforded *N*-(2-mercapto-5-oxo-oxazolidin-2-yl)-4-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzamide **10**. Reaction of **8** with anthranilic acid gave 2-{3-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]benzoyl}thioureido} benzoic acid **11**, which underwent cyclization by boiling in acetic anhydride to yield 3-(4-[4-oxo-1,2,3,4-tetrahydro-quinazolin-3-carbonyl)phenyl]-2-phenyl-quinazolin-4(3*H*)-one **12**. Reaction of **8** with 2-amino-phenol gave 2-amino-phenyl-4-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzoylcarbamothioate **13**, which cyclized with formation of *N*-(benzoyl[*d*]oxazol-2-yl)-4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]benzamide **14**. Reaction of **8** with thioglycolic acid gave 2-(4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenylcarbamothioyl-thio)acetic acid **15**, which cyclized into 3-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]benzoyl}-2-thioxothiazolidin-4-one **16** by boiling in acetic anhydride. The structures of newly synthesized derivatives were confirmed by elemental analysis and spectroscopic data.

Antimicrobial activity. Antimicrobial activity (see the table) of some synthesized compounds was screened against Gram positive bacteria *Bacillus subtilis, Rhodococcus Equi*, and the Gram-negative bacteria *Salmonella typhimurium* and *Escherichia coli*. They were also evaluated for antifungal activity against *Aspergillus Niger* and *Penicillium Notatum*. Amoxicillin and sulphadiazine were used as standard drugs. The agar diffusion method [25] was used for determination of the preliminary antibacterial and antifungal activity and the results were recorded for each tested compound as the average diameter of inhibition zones (d) of bacterial or fungal growth around the disks in millimeters at concentration of 50 mg/mL in DMSO.

The synthesized products showed higher antibacterial activity than antifungal activity. Only compounds **9** and **15** demonstrated higher antifungal activity against *Salmonella typhimurium* and compounds **3** and **4** were inactive activity against *Aspergillus Niger* and *Penicillium Notatum*.

CONCLUSIONS

Synthetic approach to the new 3(4*H*)-quinazolinone derivatives is developed. The synthesis of ethyl 4-[4-oxo-2-phenyl-quinazolin-3(4*H*)-yl]benzoate **2** and 4-(2-phenyl-4-oxo-4*H*-quinazolin-3-yl)benzoyl isothiocyanate **8** afforded the corresponding free *N*-nucleo-sides. The method is superior in simplicity and yield, compared to alternative multistep strategies that had been reported earlier. A series of 3(4*H*)-quinazolinone derivatives

were synthesized and were characterized by spectroscopic techniques. Antimicrobial activity of the title compounds was evaluated against gram positive, gram negative bacteria and fungal pathogens. Most of the synthesized derivatives demonstrated biological activity close to that of amoxicillin and sulphadiazine.

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REFERENCES

1. Kobayashi, S., Ueno, M., Suzuki, R., and Ishitani, H., *Tetrahedron Lett*., 1999, vol. 40, p. 2175. doi org/10.1016/S0040-4039(99)00142-2
2. Raju, G.N., Sai, K.B., Resshma, Sudarshini, N., Sowmya, P.L., Nalini, Y., and Nadendla, R.R., *J. Chem. and Pharm. Research*, 2015, vol. 7(5), p. 1279.
3. Gueyrard, D., Gurnel, V., Leoni, O., Palmieri, S.M., and Rollin, P., *Heterocycles*, 2000, vol. 52, p. 827. doi 10.3987/COM-99-S93
4. Cao, S.L., Feng, Y.P., Jiang, Y.P., Liu, S.Y., Ding, G.Y. and Li, R.T., *Bioorg. Chem. Lett*., 2005, vol. 15, p. 1915. doi 10.1016/j.bmcl.2005.01.083
5. Rhee, H.K., Yoo, J.H., Lee, E., Kwon, Y.J., Seo, H.R., Lee, Y.S., and Choo, H.Y., *Eur. J. Med. Chem.*, 2011, vol. 46(9), p. 3900. doi org/10.1016/j.ejmech.2011.05.061
6. Kumar, P.B.R., Murthy, S.M., and Jayaveera, K.N., *J. Pharm. Bio. Sci*., 2015, vol. 10(1), p. 30. doi org/10.21276/ijpbs
7. Rosowesy, A., Mota, C.E., and Queener, S.F., *J. Med Chem.*, 1994, vol. 37, p. 4522. doi 10.1021/jm00052a011
8. Jain, K.S., Bariwal, J.B., Kathiravan, M.K., Phoujdar, M.S., Sahne, R.S., Chauhan, B.S., Shah, A.K., and Yadav, M.R., *Bioorg. Med. Chem*., 2008, vol. 16, p. 4759. doi org/10.1016/j.bmc.2008.02.091
9. Aly, A.A. and El-Sayed, R., *Chem. Pap*., 2006, vol. 60 (1), p. 56. doi 10.2478/s11696-006-0010-3
10. Ganjee, A., Vasuderan, A., and Kisliuk, R.L., *J. Het. Chem*., 1997, vol. 34, p. 1669. doi 10.1002/jhet.5570340605
11. Hassanzadeh, F., Jafari, E., Hakimelahi, G.H., Khajouei, M.R.M., Jalali, M., and Khodarahmi, G.A., *Res. Pharm. Sci*., 2012, vol. 7(2), p. 87.
12. El-Shenawy, A.I. and Aly, A.A., *Egypt. J. Chem.*, 2005, vol. 48(6), p. 781.
13. Chao, Q., Deng, L., Shih, H., Leoni, L.M., Genini, D., Carson, D.A., and Cottam, H.B., *J. Med. Chem*., 1999, vol. 42, p. 3860. doi 10.1021/jm9805900
14. Rewcastle, G.W., Denny, W.A., Bridges, A.J., Zhou, H., Cody, D.R., McMichael, A., and Fry, D.W., *J. Med. Chem*., 1996, vol. 38, p. 482. doi 10.1021/jm00018a008
15. Glaser, T. and Traber, J., *Agents Actions*, 1984, vol. 15, p. 314. doi org/10.1007/BF01972369
16. Showalter, H.D.H., Bridges, A.J., Zhou, H., Sercel, A.D., McMichael, A., and Fry, D.W., *J. Med. Chem*., 1999, vol. 42(26), p. 5464. doi 10.1021/jm9903949
17. Navale, V., Shinde, R., Patil, S., Vibhute, A., and Zangade, S., *J. Advance Chem. Sci*., 2016, vol. 2(1), p. 201.
18. Malamas, M.S., Sredy, J., Gunawan, I., Mihan, B., Sawicki, D.R., Seestaller, I., Sullivan, D., and Flam, B.R., *J. Med. Chem*., 2000, vol. 43, p. 995. doi 10.1021/jm990476x
19. Aaglawe, M.J., Dhule, S.S., Bahekar, S.S., Wakte, P.S., and Shinde, D.B., *J. Korean Chem. Soc*., 2003, vol. 47(2), p. 133. doi org/10.5012/jkcs.2003.47.2.133
20. Pereira, E.R., Sancelme, M., Voldoire, A., and Prudhomme, M., *Bioorg. Med. Chem. Lett.*, 1997, vol. 7(19), p. 2503. doi org/10.1016/S0960-894X(97)10007-5
21. Dharmarajan, S., Perumal, Y., Murugesan, D., and Rathinasababathy, T., *J. Antimicrom. Chem*., 2007, vol. 59(6), p. 1194. doi org/10.1093/jac/dkm085
22. Havera, H.J. and Vidrio, H.J., *J. Med. Chem*., 1979, vol. 22, p. 1548. doi 10.1021/jm00198a024
23. Zhang, Y., Xu, C., Houghten, R.A., and Yu, Y., *J. Comb. Chem*., 2007, vol. 9, p. 9. doi 10.1021/cc0601231
24 Caughren, S.R., WO Patent, 1997, vol. 9, p. 749.
25. Leifert, C.S., Chidburee, H.L., Hampson, S., Workman, S., Sigee, D., Epton, H.A.S., and Harbour, A., *J. Appl. Bacteriol*., 1995, vol. 78(2), p. 97. doi 10.1111/j.1365-2672.1995.tb02829.x