# Facile Route for Novel Quinazolinone-Fused Azauracils through Cyclodesulfurization of Thioquinazolinones

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**Abstract:** An efficient, novel, short, and high-yielding one-pot protocol for the synthesis of diverse quinazolinone-fused azauracil heterocycles through cyclodesulfurization and intramolecular cyclization of thioquinazolinone using silver cyanate is described.

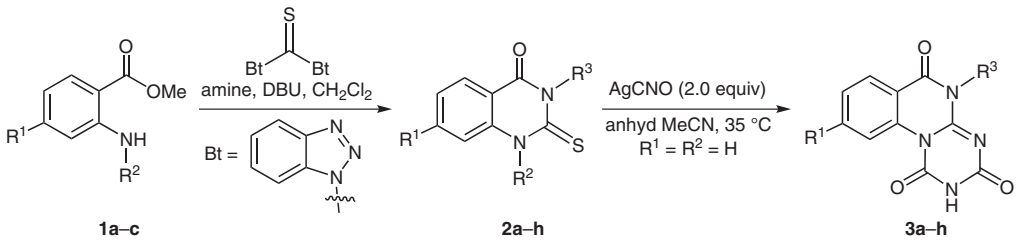
**Key words:** thioquinazolinone, cyclodesulfurization, benzotriazole, cyclization, fused heterocycles

During the last decade the search of novel compound's libraries of great chemotherapeutic values has enticed the major focus in chemical biology and medicinal chemistry and thus resulted the huge efforts to search the efficient synthetic methodologies to access small molecules of privileged structures.[1] Fused heterocyclic cores are often considered as privileged skeleton to identify the novel and potential leads in drug discovery.[2–4] Heterocyclization through cyclodesulfurization is simple and straightforward strategy for an easy access of pharmacologically important skeletons,[5] however, this has been less investigated specially for the synthesis of fused ring and to the best of our literature survey this is the first report for the synthesis of quinazolinone-fused azauracil skeletons. Quinazolinone heterocycle with simple or fused ring skeleton is very common in several naturally occurring alkaloids displaying a wide range of biological activities,[6] hence it has occupied a prominent place in finding new chemical entities in drug discovery program. In the design of a novel drug candidate, the development of hybrid molecules through the combination of different pharmacophores in a single molecule sometimes may lead to compounds with improved activity profile.

Very recently, the synthesis of diverse 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones through one-pot reaction of anthranilic acid esters, primary amines, and bis(benzotriazol-1-yl)methanethione in the presence of the amidine base DBU was developed by us.[7a,b] In addition, the synthesis of pharmacologically active novel $N^3$-substituted quinazolinone scaffolds using diverse heterocyclic amine pharmacophores such as thiazole, oxadiazole, thiadiazole under MW irradiation was also accomplished by us,[7c] where application of these developed quinazolinones in the development of fused azauracil heterocycles has not yet been disclosed. Therefore, the huge therapeutic potential as well as the lack of methodology to construct quinazolinone-fused azauracils has driven our interest to develop a simple, facile, and novel protocol for fused heterocycles by the one-pot reaction of thioquinazolinones with silver cyanate under mild reaction conditions.

Our ongoing attempt to design and develop the medicinally important scaffolds by novel routes[7–10] resulted in the development of present methodology. This synthetic strategy involves the cyclodesulfurization of thiquinozolinone by treatment with silver cyanate in anhydrous MeCN at ambient temperature.

The reaction of silver cyanate with different $N^3$-aryl/heteroaryl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one in anhydrous MeCN afforded the desired fused heterocyclic products in excellent yields (Scheme 1). The reaction was found to be clean and proceeded smoothly to yield the desired compounds without any side product. Cyclodesulfurization and intramolecular ring closure are the key steps of the reaction leading to the desired quinazolinone-fused azauracil heterocycles. Synthesized compounds were characterized on the basis of spectral data. In order to standardize the reaction parameters to obtain the optimum yield with reduced reaction time, the effect of various solvents such as toluene, benzene, $CH_2Cl_2$, THF, MeCN upon yield as well as reaction duration was investigated




**Scheme 1** Synthesis of quinazolinone-fused azauracil derivatives

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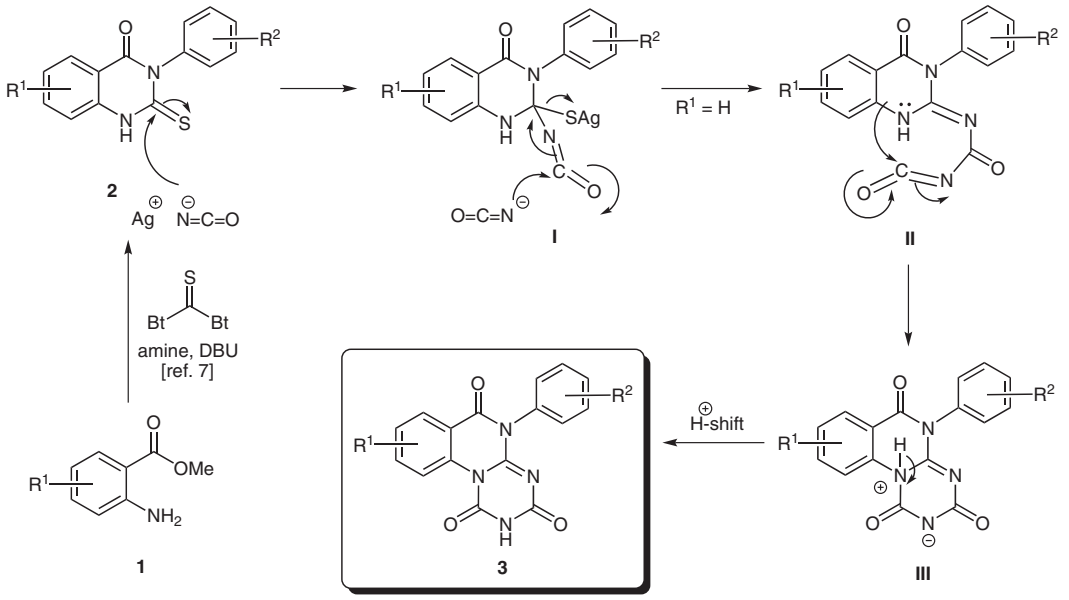



**Scheme 2** Proposed mechanism for the formation of quinazolinone-fused azauracil heterocycles

intensively. The results revealed that MeCN is the best suited solvent for cyclodesulfurization to provide the desired fused heterocycles in an excellent yield with reduced reaction time. Under the similar reaction conditions a series of diverse quinazolinone-fused azauracil heterocycles **3a–h** were synthesized in almost quantitative yield from the reaction of different $N^3$-aryl including phenyl, *p*-chlorophenyl, *p*-fluorophenyl, *p*-nitrophenyl, and other pharmacologically important pharmacophores viz. thiazole, [1,3,4]-oxadiazoles, and thiadiazole-substituted 2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones **2a–h** with silver cyanate. All the developed fused azauracils **3a–h** were purified by flash column chromatography using a gradient of ethyl acetate in *n*-hexane and characterized through spectral and elemental analysis.

The plausible reaction mechanism is proposed to proceed via the desulfurization (Scheme 2, Table 1). In the first step of the reaction, the cyanate anion attacks on the electron-deficient thione carbon of thioquinazolinone **2** leading to intermediate **I**, which on subsequent in situ attack of another cyanate anion paves the way for intermediate **2** through cyclodesulfurization. Furthermore, the intramolecular cyclization assisted by the attack of the lone-pair electron of the nitrogen of thioquinazolinone on the terminal carbonyl carbon of cyanate **II** leads to the formation of intermediate **III**, eventually followed by an H-shift from the quaternary nitrogen of thiquinazolinone to nitrogen of the uracil ring, which results in the desired quinazolinone-fused azauracil heterocycles **3** in an excellent yield.

**Table 1** Developed Quinazolinone-Fused Azauracil Heterocycles

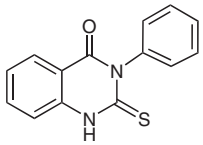
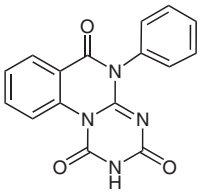
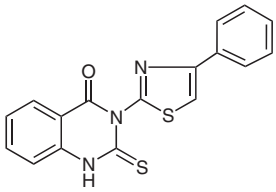
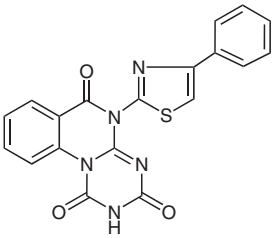
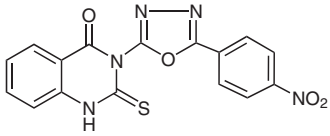
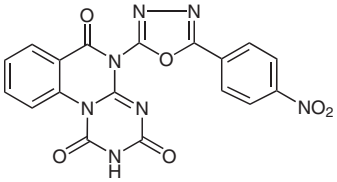
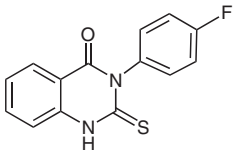
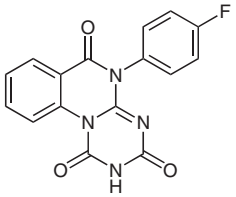
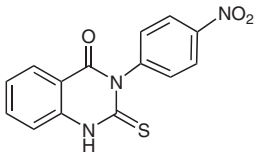
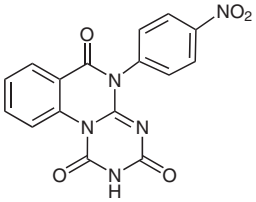
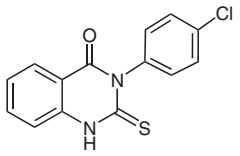
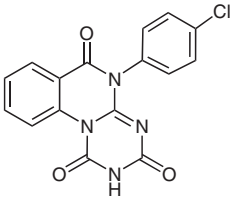
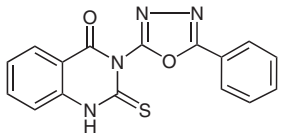
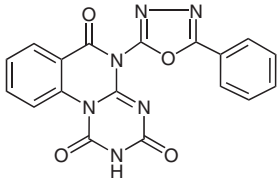
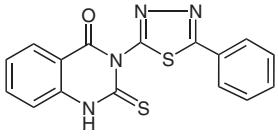
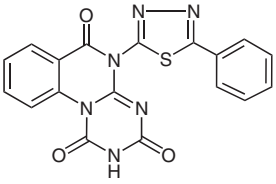
| Entry | Thioxoquinazolinone **2a–h**[a] | Quinazolinone-fused azauracil **3a–h** | Reaction conditions | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  **2a** |  **3a** | toluene, 35 °C, 60 min | 70 |
| 2 | **2a** | **3a** | $C_6H_6$, 35 °C, 60 min | 72 |
| 3 | **2a** | **3a** | $CH_2Cl_2$, 35 °C, 60 min | 70 |
| 4 | **2a** | **3a** | THF, 35 °C, 60 min | 75 |
| 5 | **2a** | **3a** | MeCN, 35 °C, 30 min | 94 |

**Table 1** Developed Quinazolinone-Fused Azauracil Heterocycles (continued)

| Entry | Thioxoquinazolinone **2a**–**h**[a] | Quinazolinone-fused azauracil **3a**–**h** | Reaction conditions | Yield (%)[b] |
|---|---|---|---|---|
| 6 |  **2b** |  **3b** | MeCN, 35 °C, 30 min | 88 |
| 7 |  **2c** |  **3c** | MeCN, 35 °C, 30 min | 91 |
| 8 |  **2d** |  **3d** | MeCN, 35 °C, 30 min | 90 |
| 9 |  **2e** |  **3e** | MeCN, 35 °C, 30 min | 90 |
| 10 |  **2f** |  **3f** | MeCN, 35 °C, 30 min | 92 |
| 11 |  **2g** |  **3g** | MeCN, 35 °C, 30 min | 92 |
| 12 |  **2h** |  **3h** | MeCN, 35 °C, 30 min | 95 |

[a] Thioxoquinazolinones **2a**–**h** were synthesized by DBU-catalyzed reaction of bis(benzotriazol-1-yl)methanethione, anthranilic acid/esters, and primary amines.[7]
[b] Yields refer to isolated pure product.

In conclusion, we have developed a simple and efficient method for an easy access to diverse novel quinazolinone-fused azauracil heterocycles through cyclodesulfurization followed by intramolecular cyclization. To the best of our knowledge the developed protocol is the first approach for the synthesis of this type of quinazolinone-fused azauracil heterocycles and offers numerous advantages such as (a) mild reaction conditions (at ambient temperature without any catalyst); (b) simple workup procedure, and (c) excellent yields of the desired products. Methodology is highly facile and may be extended for the synthesis of carbohydrate-based azauracil scaffolds of great medicinal values. This investigation is under way in our laboratory.

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## References and Notes

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(10) **Typical Experimental Procedure for the Synthesis of Quinazolinone-Fused Azauracil Compounds 3a–h**
Diverse 2-thioxo-2,3-dihydroquinazolin-4 (1*H*)-ones **2a**–**h** were obtained in good yield by the one-pot reaction of anthranilic acid/esters, primary amines, and bis(benzotriazol-1-yl)methanethione in presence of the amidine base as per ref. 7. Thioquinazolinone (**2a**, 0.5 g 1.96 mmol) was added in anhyd MeCN (8 mL) and stirred for 10 min then AgCNO (0.59 g, 3.93 mmol) was added in above solution. Solid precipitated out within 5 min and reaction mixture was further stirred for 30 min, where reaction mass turns into greenish color. Progress of reaction was monitored by TLC (25% EtOAc in *n*-hexane). After completion of reaction, product was filtered, dried, and subjected to column chromatography (25% EtOAc in *n*-hexane) to obtain pure white solid (90–95% yield).
Compound **3a**: yield 91%; mp 160–162 °C. IR (KBr): $\nu_{max}$ = 3429 (NH), 1676, 1591, 1568, 1508 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.5 Hz, 1 H), 7.83 (t, *J* = 7.2 Hz, 1 H), 7.71 (d, *J* = 8.4 Hz, 1 H), 7.43 (m, 4 H), 6.77 (m, 2 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 166.10, 161.03, 145.95, 139.88, 134.52, 129.39, 129.16, 128.14, 128.04, 126.49, 124.01, 119.64 ppm. Anal. Calcd for $C_{16}H_{10}N_4O_3$: C, 62.74; H, 3.29; N, 18.29. Found: C, 62.51; H, 3.75; N, 18.88.
Compound **3b**: yield 91%; mp 178–180 °C. IR (KBr): $\nu_{max}$ = 3431 (NH), 1669, 1596, 1569, 1511 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 11.02 (br s, 1 H, NH), 7.96 (d, *J* = 7.8 Hz, 2 H), 7.67 (t, *J* = 8.4 Hz, 2 H), 7.48 (d, *J* = 8.4 Hz, 1 H), 7.34 (t, *J* = 8.4 Hz, 1 H), 7.04 (t, *J* = 8.7 Hz, 2 H), 6.69 (s, 1 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 167.84, 162.0, 140.91, 134.79, 134.79, 133.17, 133.06, 130.66, 129.96, 126.84, 123.90, 123.41, 118.27 ppm. Anal. Calcd for $C_{19}H_{11}N_5O_3S$: C, 58.61; H, 2.85; N, 17.99. Found: C, 58.22; H, 3.01; N, 18.45.
Compound **3c**: yield 91%; mp 187–188 °C. IR (KBr): $\nu_{max}$ = 3430, 1677, 1593, 1577, 1507 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 9.82 (br s, NH, 1 H), 8.42 (d, *J* = 9.0 Hz, 2 H), 8.23 (m, 2 H), 7.77 (t, *J* = 7.8 Hz, 1 H), 7.48 (d, *J* = 8.7 Hz, 1 H), 7.38 (m, 1 H), 7.15 (d, *J* = 8.7 Hz, 1 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 165.5, 159.90, 145.33, 143.27, 137.98, 133.80, 129.00, 125.60, 124.35, 122.55, 122.42, 114.37, 114.17, 110.53 ppm.
Compound **3d**: yield 91%; mp 171–173 °C. IR (KBr): $\nu_{max}$ = 3433 (NH), 1677 (O=CN), 1622, 1529 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 8.7 Hz, 2 H), 7.99–7.89 (m, merged with *J* = 7.2 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 1 H), 7.49 (d, *J* = 8.1 Hz, 2 H), 7.33 (t, *J* = 7.5 Hz, 1 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 165.10, 159.07, 145.90, 139.54, 135.41, 130.72, 130.27, 130.17, 127.27, 126.27, 126.10, 124.39, 124.34 ppm. Anal. Calcd for $C_{16}H_9FN_4O_3$: C, 59.26; H, 2.80; N, 17.28. Found: C, 59.93; H, 2.74; N, 17.97.