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# Synthesis of novel 2,3-substituted quinazolin-4-ones by condensation of alkyl or aromatic diamines with 5-(*N*-arylimino)-4-chloro-5*H*-1,2,3-dithiazoles

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Dedicated in the memory of Professor Charles W. Rees

**Abstract**—The work described in this paper is a further example of the utility of Appel's salt in the conception of novel heterocyclic rings. We confirmed that primary alkyldiamines may react easily with the methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-anthranilates to afford quinazolines, which are very interesting starting materials for the access to novel 2,3-condensed quinazolin-4-ones. On the other side, aromatic amines allow the synthesis of polycyclic molecules, which are structurally close to the model natural products (e.g., rutaecarpine, luotonine, tryptanthrine and vasicinone).


## 1. Introduction

The quinazolin-4-one skeleton, when selectively functionalized, is a building block for the preparation of numerous alkaloids and substances with pronounced biological properties, for example, anticancer, diuretic, antiinflammatory, anticonvulsant and antihypertensive activities.[1] As a part of our ongoing research activity, we launched a research programme dealing with the preparation and pharmacological evaluation of some original quinazoline derivatives, which possess a quinazolin-4-one moiety fused with another ring system as described in various terrestrial natural alkaloids among which rutaecarpine,[2] luotonine A,[3] tryptanthrine[4] and vasicinone[5] are the most studied (Fig. 1).

Thus, studying the chemistry of 4,5-dichloro-1,2,3-dithiazolium chloride (**1**) (Appel's salt[6]) and its derivatives, we recently discovered that treatment of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-anthranilates with ethylene diamine gave a rapid and easy access to novel 3,4-dihydro-2*H*-pyrazino[2,1-*b*]quinazolines (**3a–d**) mainly accompanied by variable amounts of the known 2,3-dihydro-1*H*-imidazo-[2,1-*b*]quinazolin-5-one derivatives (**4a–d**) (Scheme 1).[7] The mechanism suggested for this reaction implied existence of intermediate quinazolines (e.g., **5** in Scheme 1) and a final nucleophilic attack of the primary amino group on the carbonitrile carbon to generate the cyclic amidines, whilst nucleophilic substitution of the cyano group leads to the five-membered derivatives (such a mechanism is confirmed by the results obtained by Kim's group, which studied the reaction of ethanolamine and compound **2a**).[8] After establishment of the 3D structure of the amidines (**3**), we observed that condensation of these key intermediates with anthranilic acid led to various bis-quinazolines (**6a–c**) via a modified Niementowski reaction.[7]

Exploring the best conditions for the synthesis of various amidines, (e.g., **3**) we recently isolated a third category of products (**7**), which were identified as dimers of quinazolin-4-ones. The isolated yields of these novel molecules (**7a–c**) are low and very difficult to control, but their presence confirms the existence of the intermediate compounds (**5**).

Although a wide range of 2,3-condensed (3*H*)-quinazolin-4-ones occur in different families of plants and microorganisms, a few papers described the synthesis and the reactivity of such ring systems.[1] Novel derivatives like **3a–d** can be employed as intermediates in the synthesis of the expected bioactive compounds. Consequently, one of our actual challenges is to study the chemical behaviour of the starting imino-1,2,3-dithiazoles with alkanediamines and to vary the length of the carbon chain between the two functions. Pursuing our efforts, we also explored the possibility to condense aromatic or semi-aromatic diamines with the imines. This paper describes the scope and limitations for the access to

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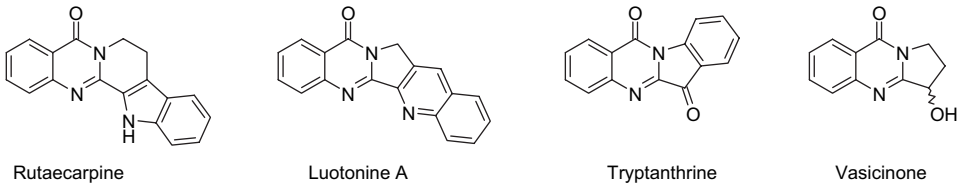
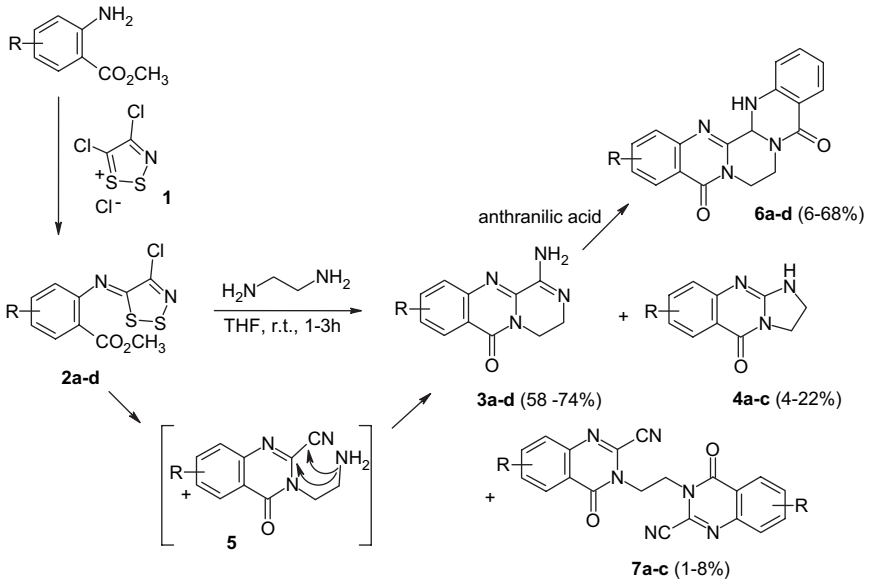



**Figure 1**.




**Scheme 1**. Reaction of imino-1,2,3-dithiazoles (**2a–d**) with ethylene diamine and preparation of compounds **3**, **4** and **7**. Reagents and conditions: ethylene diamine (1 equiv), tetrahydrofuran (THF), rt.

novel quinazolines via 5-(*N*-arylimino)-4-chloro-5*H*-1,2,3-dithiazoles obtained by Appel's salt chemistry.

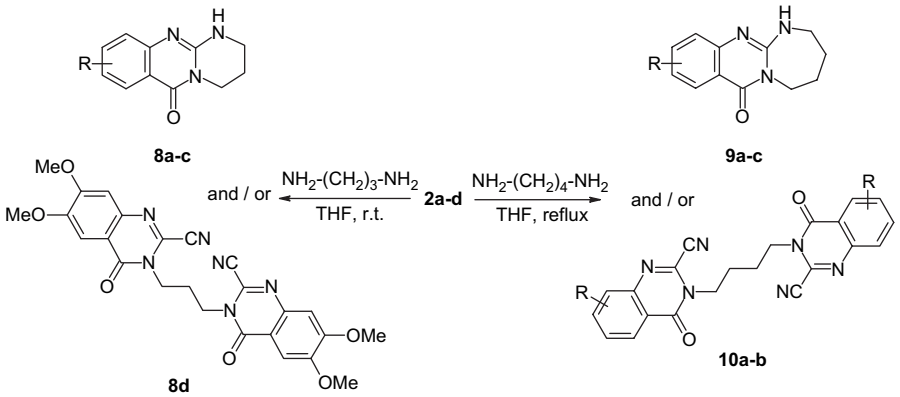
## 2. Results and discussion

### 2.1. Synthesis of the starting imino-1,2,3-dithiazoles

Following the usual methods,[9] treatment of methyl anthranilates with 4,5-dichloro-1,2,3-dithiazolium chloride **1** in dichloromethane at room temperature gave the corresponding methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-anthranilates (**2a–d**) in quantitative yields.

### 2.2. Reaction with 1,3-propane- and 1,4-butanediamine

Extension of the carbon chain between the two amines was explored using the methodology described for 1,2-ethanediamine.[7] Reaction of **2a–d** with 1 equiv of 1,3-propanediamine at room temperature was performed and afforded good yields of only one family of cyclized and stable products (**8a–c**), which result from the substitution of the cyano group by nucleophilic attack of the aliphatic amine of the intermediate quinazolin-4-ones. Here again, the dimethoxy anthranilate derivative (**2d**) behaved differently than the other compounds and gave only small amounts of a dimer (**8d**) (Scheme 2 and Table 1).




**Scheme 2**. Reaction of imino-1,2,3-dithiazoles (**2a–d**) with 1,3-propane- or 1,4-butanediamine. Reagents and conditions: diamine (1 equiv), THF, 3 h.

**Table 1**. Reaction of imino-esters (**2a–d**) with 1,3-propane- or 1,4-butanediamines

| Starting ester (R) | Yield of **8** (%) | Yield of **9** (%) | Yield of **10** (%) |
|---|---|---|---|
| **a** (H) | 56 | 4 | 3 |
| **b** (5-Br) | 86 | 4 | 7 |
| **c** (4-Cl) | 81 | 45 | — |
| **d** (4,5-diOMe) | 7 | — | — |

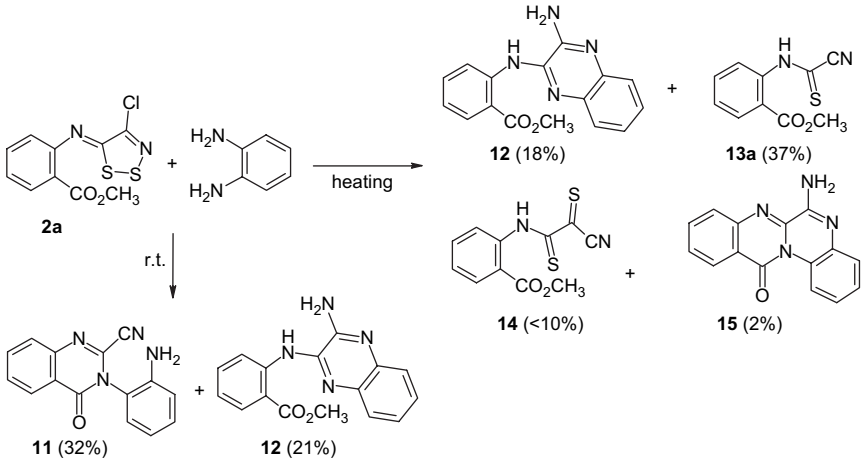
Pursuing our strategy, the iminodithiazole precursors (**2a–d**) were heated in the presence of 1 equiv of 1,4-butanediamine. In these cases, experiments at room temperature did not give any results and a large part of the starting material was retrieved. The resulting products (**9** and **10**) were difficult to isolate and the yields were quite low, showing the difficulty for the intermediate quinazoline to cyclize and to fuse a seven-membered ring with the quinazoline skeleton. Curiously the chloro-derivative (**2c**) gave an interesting yield of the attempted product (**9c**, 45%) with no traces of dimer. In these reactions, the dimers can be considered as the major products although low yields were obtained. Whatever method was experimented, and in accordance with results described above, no trace of products **9d** and **10d** was detected from the methyl ester (**2d**).

### 2.3. Condensation with arene- and semi-arene diamines

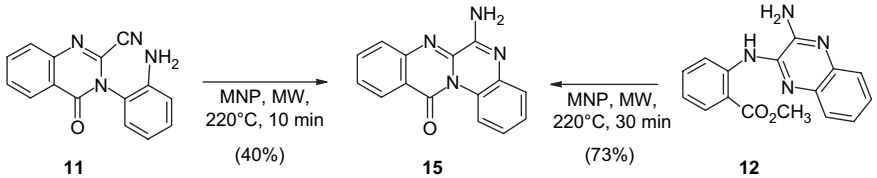
The second part of our work consisted of extending the family of the amines studied to arene or semi-arene diamines. We decided to investigate the reaction of the imino-1,2,3-dithiazoles (**2**) with *o*-phenylenediamine and *o*-aminophenethylamine. In these reactants the distance between the two amine functions is similar to those observed with the aliphatic 1,2-ethane or 1,3-propanediamines. Compared with the preceding examples, the expected cyclized products will possess a tetracyclic skeleton.

**2.3.1. Reaction with *o*-phenylenediamine.** As it was previously described in various preliminary studies, the less nucleophilic aromatic amines have some difficulties in reacting with the starting iminodithiazoles. In preliminary experiments, heating of imine **2a** and the aromatic diamine in the presence of pyridine gave only traces of a cyclized 3-(2-aminophenyl)quinazolin-4-one-2-carbonitrile (**11**). Improvement was expected by changing the reaction parameters (times of heating, heating mode, atmospheric or pressurized experiments) but the yields observed were quite variable. Changing the solvent (THF instead of pyridine) and stirring time (from 2 to 24 h) of the reaction mixture, at room temperature, gave a 32% yield of the attempted compound (**11**) accompanied by interesting amount (21%) of another product, which was identified as the 2-aminoquinoxaline (**12**). Prolonged heating (24 h) of the starting molecules afforded modest yield (18%) of the quinoxaline (**12**), accompanied by quite an important amount (37%) of cyanothioformamide (**13a**) (Scheme 3). It should be noticed that, in this case, variable amounts of dithioxamide (**14**) (<10%) were also detected, accompanied by traces (2%) of the cyclized product (**15**).

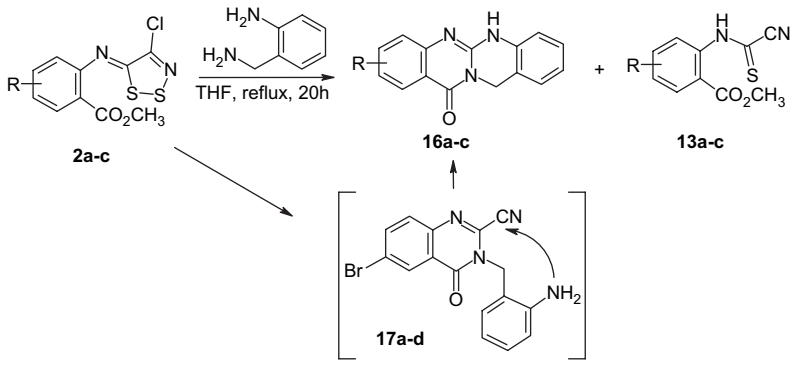
The hypothesis that quinazolin-4-one (**11**) and quinoxaline (**12**) derivatives may be the precursors of the tetracyclic 6-amino-5,7,12a-triaza-benzo[*a*]anthracen-12-one (**15**) was confirmed by strong heating of these two partners separately at 220 °C for 10–30 min under microwave irradiation in sealed tubes (Scheme 4). The synergic effect of microwaves and pressure gave convenient yields of the final molecule (**15**), 40% and 73% respectively from **11** and **12**. In a preliminary experiment we also observed that heating the starting quinazoline **11** at 110 °C in acidic conditions (HBr) gave a 39% yield of the 6-amino-5,7,12a-triaza-benzo[*a*]anthracen-12-one (**15**).




**Scheme 3**. Conditions and yields: (a) THF, rt, 24 h (**11**: 32% and **12**: 21%) or (b) THF, reflux, 24 h (**12**: 18%, **13a**: 37%, **14**: <10% and **15**: 2%).




**Scheme 4**.




**Scheme 5**. Synthesis of the fused quinazolines (**16a–c**) from imino-1,2,3-dithiazoles (**2a–c**). Reagents and conditions: THF, reflux, 20 h. For yields see Table 2.

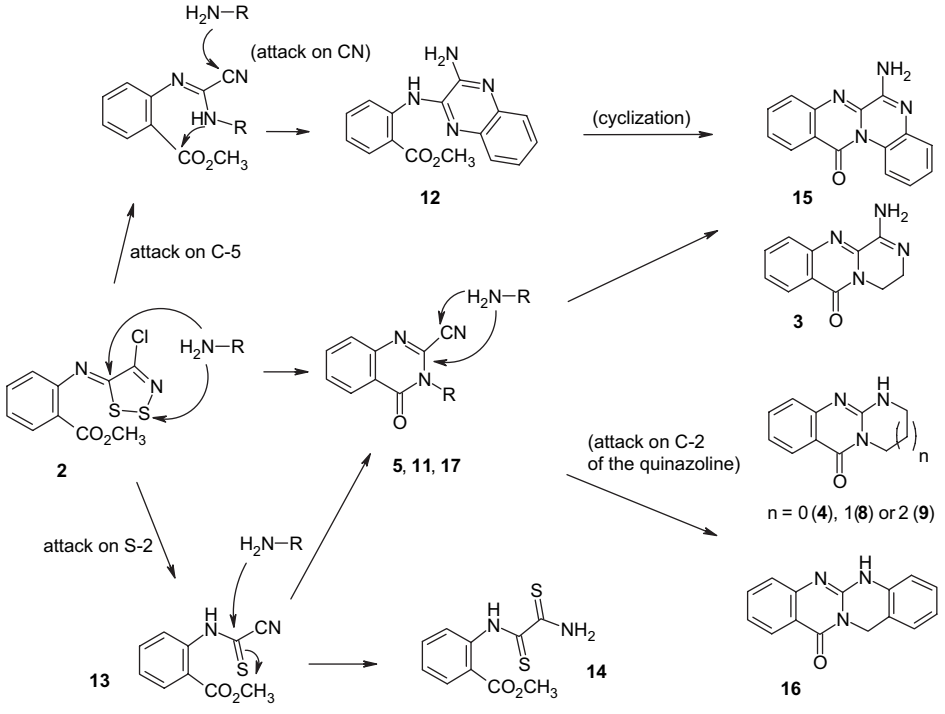
**2.3.2. Reaction with *o*-aminophenethylamine.** By comparison with the preceding example, the diamine studied in this paragraph possesses an aromatic amino group associated with an aliphatic amine. Keeping in mind the results obtained above, we discovered that heating of imines **2a–c** and *o*-aminophenethylamine (2 equiv) in THF allowed the synthesis of novel heterocyclic skeletons (**16a–c**) in which two quinazoline rings are fused. The tetracyclic products (**16a–c**) are certainly obtained via intermediate *N*-substituted quinazolin-4-ones (**17a–c** in Scheme 5), generated after a first attack of the most nucleophilic aliphatic amino group of the semi-arenediamine. This hypothesis was confirmed when stirring **2b** and *o*-aminophenethylamine at room temperature for four days, gave a 30% yield of the uncyclized quinazoline **17b**, which cyclized into the corresponding product **16b** after heating in acidic conditions (HBr). In all the experiments, a convenient amount (47–68%) of the cyanothioformamides (**13a–c**) was obtained (Scheme 5, Table 2). It should be noticed that prolonged heating of **13b** in the presence of *o*-aminophenethylamine, using the conditions described above, yielded **16b** and **17b** in modest yields (5%).

**Table 2**. Reaction of imino-esters (**2a–c**) with *o*-aminophenethylamine

| Starting ester (R) | Yield of **13** (%) | Yield of **16** (%) |
|---|---|---|
| **a** (H) | 47 | 14 |
| **b** (5-Br) | 68 | 9 |
| **c** (4-Cl) | 52 | 13 |

## 2.4. Discussion

Considering the results obtained in this paper and those previously published by our team[7,9,10] and Kim's group[11] before, it is now possible to describe the most probable mechanism of the reaction between alkane- or areneamines and the starting imino-1,2,3-dithiazoles. We suggest that




**Scheme 6**. Suggested mechanism of the action of various amines on the imino-1,2,3-dithiazoles.

most nucleophilic amines (e.g., alkaneamines or alkanediamines) will attack firstly on C-5 of the dithiazole ring and then give the intermediates quinazolin-4-ones (e.g., **6** in Scheme 1) suggested in the first part of this work. The final cyclization observed in the case of diamines may occur by attack of the second amino group on C-2 of the quinazoline (compounds **4**, **7**, **9** and **16**) or on the carbonitrile group (compounds **3** and **15**) (Scheme 6).

On the other hand, less nucleophilic amines (e.g., areneamines or diamines and also bulky amines in Kim's work) will attack on S-2 of the ring and lead to the intermediate cyanothioformamides (**13**), which can be transformed into the cyanoamidines (**6**, **17**) or into the unexpected thioxamides (**14**), as we previously published in similar examples.[1]

A preliminary evaluation of the potential biological activity of all the compounds described in this paper was realized by Meijer's group, in the *Station Biologique de Roscoff, France*, on three protein kinases, CDK1/cyclin B, CDK5/p25 and GSK-3α,β.[13–15] Among all the molecules tested, none exhibit a significant inhibitory activity against the target kinases.

## 3. Conclusion

The work described in this paper is a further example of the utility of Appel's salt in the conception of novel heterocyclic rings. We confirmed that methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-anthranilates are very interesting starting materials for the access to novel *N*-substituted quinazolin-4-one derivatives. Primary alkyldiamines may react easily with the iminodithiazole rings to afford quinazolines, which can have different behaviours as precursors of a large family of 2,3-condensed quinazolines, whilst aromatic amines allow the synthesis of polycyclic molecules, which are structurally close to the model natural products (e.g., rutaecarpine, luotonine, tryptanthrine and vasicinone).

## 4. Experimental

### 4.1. Chemistry

Commercial reagents were used as received without additional purification. Melting points were measured using a Kofler melting point apparatus and are uncorrected (mp>260 °C means that the compound does not melt on Kofler melting point apparatus). IR spectra were recorded on a Perkin–Elmer Paragon 1000PC FT-IR instrument. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) were recorded with a JEOL JNM LA400 spectrometer. Chemical shifts ($\delta$ values) are expressed in parts per million downfield from tetramethylsilane as an internal standard and coupling constants ($J$) are expressed in hertz. Mass spectra were recorded on Spectrometer simple quad platform LC micromass, electrospray. Thin-layer chromatography (TLC) was performed on 0.2 mm precoated plates of silica gel 60F-264 (Merck). Visualization was made with ultraviolet light. Column chromatography was performed by using Merck silica gel (70–230 mesh). High-resolution mass measurements were performed on a Varian MAT 311 in the *Centre Régional de Mesures Physiques de l'Ouest* (*CRMPO, Université de Rennes*).

Microwave heating was performed in a Smith-Synthesizer™ (Personal Chemistry, AB) single mode cavity, producing controlled irradiation at 2450 MHz (a detailed description of this microwave reactor with integrated robotics was recently published.[16] Reaction temperature and pressure were determined using the built-in, on-line IR and pressure sensors. Microwave assisted reactions were performed in sealed Smith process vials (0.5–5 mL, total volume 10 mL) under air with magnetic stirring. The software algorithm regulates the microwave output power so that the selected maximum temperature was maintained for the desired reaction/irradiation time. After the irradiation period, the reaction vessel was cooled rapidly to ambient temperature by compressed air (gas-jet cooling). The minimal reaction times were determined by performing sequential series of identical reactions at constant temperature and with continuous heating, but with different irradiation times. Completion of the reaction was estimated by TLC after each individual heating period.

### 4.2. Reaction with alkanediamines, synthesis of compounds 3–10

Spectral data for compounds **2a–d** are consistent with structures published separately in Ref. 7.

**4.2.1. Reaction with 1,2-ethylene diamine, synthesis of compounds 7a–c from esters 2a–c.** A solution of ethylene diamine (0.11 g, 1.71 mmol) in tetrahydrofuran (THF) (10 mL) was added slowly to a solution of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-anthranilate (**2a–c**) (1.71 mmol) in THF (10 mL). The mixture was stirred for 3 h at room temperature under inert atmosphere (argon). After evaporation of the solvent under reduced pressure, column chromatography on silica gel with dichloromethane/methanol (9:1, v/v) as solvent gave products **3**, **4** and **7** as solids.

Spectral data for compounds **3** and **4** are consistent with structures published in Ref. 7.

**4.2.1.1. Bis-3-methylene-4-oxo-3,4-dihydroquinazoline-2-carbonitrile (7a).** White solid (6%); mp>260 °C; IR (KBr) $\nu$ 779, 1583, 1683, 2240, 2965 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) $\delta$ 4.67 (s, 4H), 7.69 (td, $J$=1.60 Hz and $J$=8.00 Hz, 2H), 7.82 (d, $J$=8.00 Hz, 2H), 7.95 (td, $J$=1.60 Hz and $J$=8.00 Hz, 2H), 8.08 (dd, $J$=1.60 Hz and $J$=8.00 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 44.67, 111.46, 121.86, 126.38, 128.00, 130.20, 131.78, 135.50, 145.60, 159.79; MS (*m*/*z*) 368; HRMS (EI) $[M]^{+\bullet}$ ($C_{20}H_{12}N_6O_2$): calcd 368.1022; found 368.1035.

**4.2.1.2. Bis-6-bromo-3-methylene-4-oxo-3,4-dihydroquinazoline-2-carbonitrile (7b).** White solid (1%); mp>260 °C; IR (KBr) $\nu$ 841, 1382, 1467, 1581, 1688, 2244, 3088 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) $\delta$ 4.65 (s, 4H), 7.79 (d, $J$=8.80 Hz, H-8), 8.12 (dd, $J$=2.80 Hz and $J$=8.80 Hz, H-7), 8.18 (d, $J$=2.80 Hz, H-5); MS (*m*/*z*) 524; HRMS (EI) $[M]^{+\bullet}$ ($C_{20}H_{10}N_6O_2Br_2$): calcd 523.9232; found 523.9219.

**4.2.1.3. Bis-7-chloro-3-methylene-4-oxo-3,4-dihydroquinazoline-2-carbonitrile (7c).** White solid (8%); mp>260 °C; IR (KBr) $\nu$ 781, 1580, 1706, 2248, 3015, 3107 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 4.66 (s, 4H), 7.75 (dd, $J$=2.00 Hz and $J$=8.00 Hz, H-6), 7.94 (d, $J$=2.00 Hz, H-8), 8.09 (d, $J$=8.00 Hz, H-5); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 45.23, 111.68, 121.13, 127.69, 128.91, 130.99, 133.46, 140.84, 147.03, 159.84; MS (*m*/*z*) 436; HRMS (EI) $[M]^{+\bullet}$ ($C_{20}H_{10}N_6O_2Cl_2$): calcd 436.0242; found 436.0238.

**4.2.2. Reaction with 1,3-propanediamine, synthesis of compounds 8a–d from esters 2a–d.** A solution of 1,3-propanediamine (1.71 mmol) in tetrahydrofuran (THF) (10 mL) was added slowly to a solution of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-anthranilate (**2a–d**) (1.71 mmol) in THF (10 mL). The mixture was stirred for 3 h at room temperature under inert atmosphere (argon). After evaporation of the solvent under reduced pressure, column chromatography on silica gel with dichloromethane/ethyl acetate (8:2, v/v) as eluent gave products **8a–d** as solids.

**4.2.2.1. 1,2,3,4-Tetrahydro-1,4a,9-triazaanthracen-10-one (8a).** Brown solid (56%); mp>260 °C; IR (KBr) $\nu$ 761, 1097, 1309, 1486, 1626, 1679, 3163 $cm^{-1}$; $^1H$ NMR ($CDCl_3$+$D_2O$) $\delta$ 2.05–2.20 (m, 2H), 3.52 (t, $J$=6.00 Hz, 2H), 4.12 (t, $J$=6.00 Hz, 2H), 7.12 (t, $J$=7.60 Hz, 1H), 7.20 (d, $J$=8.00 Hz, 1H), 7.53–7.58 (m, 1H), 8.11 (dd, $J$=1.60 Hz and $J$=8.00 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.65, 39.57, 39.79, 116.73, 122.04, 123.54, 127.06, 134.46, 149.47, 149.72, 162.24; MS (*m*/*z*) 201; HRMS (EI) $[M]^{+\bullet}$ ($C_{11}H_{11}N_3O$): calcd 201.0902; found 201.0897.

**4.2.2.2. 6-Bromo-1,2,3,4-tetrahydro-1,4a,9-triazaanthracen-10-one (8b).** White solid (86%); mp>260 °C; IR (KBr) $\nu$ 732, 1483, 1623, 1690, 2884, 2972, 3254 $cm^{-1}$; $^1H$ NMR ($CDCl_3$+$D_2O$) $\delta$ 2.05–2.15 (m, 2H), 3.49 (t, $J$=5.80 Hz, 2H), 4.10 (t, $J$=5.80 Hz, 2H), 7.09 (d, $J$=8.80 Hz, H-8), 7.59 (dd, $J$=2.40 Hz and $J$=8.80 Hz, H-7), 8.21 (d, $J$=2.40 Hz, H-5); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.44, 39.38, 39.93, 114.44, 118.01, 125.46, 129.38, 137.46, 148.38, 149.93, 161.15; MS (*m*/*z*) 279; HRMS (EI) $[M]^{+\bullet}$ ($C_{11}H_{10}N_3OBr$): calcd 279.0007; found 279.0016.

**4.2.2.3. 7-Chloro-1,2,3,4-tetrahydro-1,4a,9-triazaanthracen-10-one (8c).** White solid (81%); mp>260 °C; IR (KBr) $\nu$ 684, 910, 1167, 1597, 1630, 1688, 2976, 3150 $cm^{-1}$; $^1H$ NMR ($CDCl_3$+$D_2O$) $\delta$ 2.05–2.20 (m, 2H), 3.52 (t, $J$=6.00 Hz, 2H), 4.10 (t, $J$=6.00 Hz, 2H), 7.06 (dd, $J$=2.00 Hz and $J$=8.20 Hz, H-6), 7.19 (d, $J$=2.00 Hz, H-8), 8.02 (d, $J$=8.20 Hz, H-5); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.40, 39.42, 39.76, 115.04, 122.55, 122.76, 128.55, 140.50, 150.35, 150.52, 161.59; MS (*m*/*z*) 235; HRMS (EI) $[M]^{+\bullet}$ ($C_{11}H_{10}N_3OCl$): calcd 235.0512; found 235.0503.

**4.2.2.4. 1,3-Di[3-(2-cyano-6,7-dimethoxy 4-oxo-3,4-dihydroquinazoline)]propane (8d).** White solid; mp>260 °C; IR (KBr) $\nu$ 872, 1280, 1500, 1691, 2238, 2928 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.42–2.52 (m, 2H), 4.02 (br s, 12H, 4×$CH_3$), 4.47 (t, $J$=7.00 Hz, 4H,), 7.16 (s, 2H), 7.60 (s, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 27.27, 43.61, 55.97, 56.20, 105.30, 108.44, 112.00, 115.86, 130.11, 141.89, 150.85, 154.91, 158.65; MS (*m*/*z*) 502; HRMS (EI) $[M]^{+\bullet}$ ($C_{25}H_{22}N_6O_6$): calcd 502.1601; found 502.1612.

**4.2.3. Reaction with 1,4-butanediamine, synthesis of compounds 9a–c and 10a,b from esters 2a–c.** A solution of 1,4-butanediamine (1.71 mmol) in tetrahydrofuran (THF) (10 mL) was added slowly to a solution of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-anthranilate (**2a–d**) (1.71 mmol) in THF (10 mL). The mixture was stirred at reflux for 3 h under inert atmosphere (argon). After cooling and evaporation of the solvent under reduced pressure, column chromatography on silica gel with dichloromethane/ethyl acetate (8:2, v/v) as eluent gave products **9a–d** and **10a**,**b** as solids.

**4.2.3.1. 7,8,9,10-Tetrahydro-6*H*-5,6,10a-triazacyclohepta[*b*]naphthalen-11-one (9a).** Yellow solid (4%); mp=125 °C; IR (KBr) $\nu$ 1492, 1690, 2862, 3238 $cm^{-1}$; $^1H$ NMR ($CDCl_3$+$D_2O$) $\delta$ 1.82–1.97 (m, 4H), 3.28–3.38 (m, 2H), 4.32 (t, $J$=6.00 Hz, 2H), 7.23–7.30 (m, 1H), 7.34 (d, $J$=8.00 Hz, 1H), 7.62 (td, $J$=1.60 Hz and $J$=8.00 Hz, 1H), 8.16 (dd, $J$=1.60 Hz and $J$=8.00 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 25.88, 27.12, 43.54, 45.83, 77.67, 118.22, 123.82, 124.61, 127.26, 134.45, 156.05, 163.36; MS (*m*/*z*) 215; HRMS (EI) $[M]^{+\bullet}$ ($C_{12}H_{13}N_3O$): calcd 215.1057; found 215.1051.

**4.2.3.2. 2-Bromo-7,8,9,10-tetrahydro-6*H*-5,6,10a-triazacyclohepta[*b*]naphthalen-11-one (9b).** White solid (4%); mp=162 °C; IR (KBr) $\nu$ 827, 1470, 1601, 1655, 2853, 2935, 3324 $cm^{-1}$; $^1H$ NMR ($CDCl_3$+$D_2O$) $\delta$ 1.85–1.95 (m, 4H), 3.28–3.38 (m, 2H), 4.31 (t, $J$=5.60 Hz, 2H), 7.21 (d, $J$=8.80 Hz, H-4), 7.67 (dd, $J$=1.60 Hz and $J$=8.80 Hz, H-3), 8.28 (d, $J$=1.60 Hz, H-1); $^{13}C$ NMR ($CDCl_3$) $\delta$ 25.72, 26.92, 43.74, 45.71, 116.51, 119.56, 126.58, 129.64, 137.44, 147.33, 156.23, 162.29; MS (*m*/*z*) 293; HRMS (EI) $[M]^{+\bullet}$ ($C_{12}H_{12}N_3OBr$): calcd 293.0164; found 293.0169.

**4.2.3.3. 3-Chloro-7,8,9,10-tetrahydro-6*H*-5,6,10a-triazacyclohepta[*b*]naphthalen-11-one (9c).** White solid (45%); mp=200 °C; IR (KBr) $\nu$ 784, 1602, 1684, 2944, 3180, 3224 $cm^{-1}$; $^1H$ NMR ($CDCl_3$+$D_2O$) $\delta$ 1.85–1.95 (m, 4H), 3.32 (t, $J$=6.00 Hz, 2H), 4.30 (t, $J$=6.00 Hz, 2H), 7.18 (dd, $J$=2.00 Hz and $J$=8.40 Hz, H-2), 7.32 (d, $J$=2.00 Hz, H-4), 8.07 (d, $J$=8.40 Hz, H-1); $^{13}C$ NMR ($CDCl_3$) $\delta$ 25.64, 26.80, 43.55, 45.59, 116.53, 124.10, 124.26, 128.69, 140.49, 149.26, 156.74, 162.77; MS (*m*/*z*) 249; HRMS (EI) $[M]^{+\bullet}$ ($C_{12}H_{12}N_3OCl$): calcd 249.0669; found 249.0653.

**4.2.3.4. Bis-3-ethylene-4-oxo-3,4-dihydroquinazoline-2-carbonitrile (10a).** White solid (3%); mp>260 °C; IR (KBr) $\nu$ 775, 1267, 1582, 1694, 2240, 2945 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.00–2.15 (m, 4H), 4.40–4.50 (m, 4H), 7.66 (td, $J$=1.40 Hz and $J$=7.60 Hz, 2H), 7.78–7.88 (m, 4H), 8.32 (dd, $J$=1.40 Hz and $J$=7.60 Hz, 2H,); $^{13}C$ NMR ($CDCl_3$) $\delta$ 26.35, 45.79, 111.49, 122.63, 127.14, 128.55, 130.16, 131.17, 135.20, 146.32, 159.95; MS (*m*/*z*) 396; HRMS (EI) $[M]^{+\bullet}$ ($C_{22}H_{16}N_6O_2$): calcd 396.1335; found 396.1351.

**4.2.3.5. Bis-6-bromo-3-ethylene-4-oxo-3,4-dihydroquinazoline-2-carbonitrile (10b).** White solid (7%); mp>260 °C; IR (KBr) $\nu$ 676, 828, 1325, 1576, 1695, 2246, 2944, 3085 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 1.80–1.90 (m, 4H), 4.20–4.30 (m, 4H), 7.77 (d, $J$=8.60 Hz, 2H), 8.09 (dd, $J$=2.40 Hz and $J$=8.60 Hz, 2H), 8.27 (d, $J$=2.40 Hz, 2H); MS (*m*/*z*) 552; HRMS (EI) $[M]^{+\bullet}$ ($C_{22}H_{14}N_6O_2Br_2$): calcd 551.9545; found 551.9525.

### 4.3. Reaction with *o*-phenylenediamine, synthesis of compounds 11–15 from ester 2a

A solution of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-yliden)-methyl-benzoate (**2a**) (0.35 g, 1.22 mmol) and *o*-phenylenediamine (0.26 g, 2.44 mmol) in tetrahydrofuran (20 mL) was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel with dichloromethane/ethyl acetate (9:1, v/v) as eluent to furnish **11** (32%) and **12** (21%). The same procedure was realized at reflux for 24 h and gave, after purification, compounds **12** (18%), **13a** (37%), **14** (<10%) and **15** (2%).

**4.3.1. 3-(2-Aminophenyl)-4-oxo-3,4-dihydroquinazoline-2-carbonitrile (11).** Yellow solid (32%); mp>260 °C; IR (KBr) $\nu$ 559, 1278, 1340, 1634, 1681, 2241, 3362, 3450 $cm^{-1}$; $^1H$ NMR ($CDCl_3$+$D_2O$) $\delta$ 6.96–7.00 (m, 2H), 7.18 (d, $J$=8.00 Hz, 1H), 7.39 (t, $J$=8.00 Hz, 1H), 7.68–7.72 (m, 1H), 7.88–7.94 (m, 2H), 8.39 (d, $J$=8.00 Hz, 1H); MS (*m*/*z*) 262; HRMS (EI) $[M]^{+\bullet}$ ($C_{15}H_{10}N_4O$): calcd 262.0855; found 262.0844.

**4.3.2. 2-(3-Aminoquinoxalin-2-ylamino)-benzoic acid methyl ester (12).** Yellow solid (18–21%); mp=198 °C; IR (KBr) $\nu$ 744, 1258, 1431, 1593, 1690, 2950, 3135, 3405 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$+$D_2O$) $\delta$ 3.80 (s, 3H), 7.15 (t, $J$=7.60 Hz, 1H), 7.26–7.35 (m, 2H), 7.46–7.52 (m, 2H), 7.63–7.67 (m, 1H), 7.95–7.97 (m, 1H), 8.52 (d, $J$=8.40 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 52.01, 117. 62, 121.61, 124.09, 124.51, 125.39, 125.56, 130.41, 135.64, 137.73, 141.34, 146.35, 167.60; MS (*m*/*z*) 294; HRMS (EI) $[M]^{+\bullet}$ ($C_{16}H_{14}N_4O_2$): calcd 294.1117; found 294.1104.

Spectral data for compounds **13a** and **14** are consistent with structures published in Refs. 10 and 12.

**4.3.3. 6-Amino-5,7,12a-triaza-benzo[*a*]anthracen-12-one (15).** In a sealed vial, a solution of quinazolinone **11** or **12** (0.06 g, 0.30 mmol) in MNP (3 mL) was heated under microwave irradiation at 220 °C during 30 min. After cooling, the solution was diluted with ethyl acetate (10 mL) and washed with water (3×10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel with dichloromethane/ethyl acetate (9:1, v/v) as eluent to give compound **15** as white solid (40% from **11** and 73% from **12**); mp>260 °C; IR (KBr) $\nu$ 760, 1290, 1562, 1658, 1700, 3098, 3446 $cm^{-1}$; $^1H$ NMR ($CDCl_3$+$D_2O$) $\delta$ 7.32 (td, $J$=1.50 Hz and $J$=7.80 Hz, 1H), 7.42–7.48 (m, 1H), 7.56 (dd, $J$=1.50 Hz and $J$=7.80 Hz, 1H), 7.60–7.67 (m, 1H), 7.80–7.91 (m, 2H), 8.50 (d, $J$=7.80 Hz, 1H), 9.50 (d, $J$=8.80 Hz, 1H); MS (*m*/*z*) 262; HRMS (EI) $[M]^{+\bullet}$ ($C_{15}H_{10}N_4O$): calcd 262.0854; found 262.0836.

### 4.4. Reaction with *o*-aminophenethylamine, synthesis of compounds 16a–c and 17b from esters 2a–c

A solution of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-yliden)-methyl-benzoate (**2a–c**) (1.19 mmol) and 2-aminophenethylamine (0.29 g, 2.38 mmol) in tetrahydrofuran (20 mL) was refluxed for 20 h in an oil bath. Upon cooling, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel with dichloromethane/ethyl acetate (80:20, v/v) as eluent to furnish **16a–c** and cyanothioformamides **13a–c**. The same procedure was realized from **2b** at room temperature for four days and afforded **17b** in a modest yield (5%).

Spectral data for compounds **13a–c** are consistent with structures published in Ref. 7.

**4.4.1. 5,12-Dihydro-5,6,11a-triazanaphthacen-11-one (16a).** White solid (47%); mp>260 °C; IR (KBr) $\nu$ 755, 1483, 1556, 1681, 3228 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$+$D_2O$) $\delta$ 5.12 (s, 2H), 6.99–7.00 (m, 2H), 7.10–7.25 (m, 2H), 7.25–7.35 (m, 2H), 7.63 (d, $J$=7.60 Hz, 1H), 7.97 (d, $J$=7.60 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 42.54, 113.84, 116.42, 117.72, 121.85, 122.58, 124.34, 126.38, 126.44, 128.37, 134.44, 135.63, 146.47, 149.00, 161.21; MS (*m*/*z*) 249; HRMS (EI) $[M]^{+\bullet}$ ($C_{15}H_{11}N_3O$): calcd 249.09021; found 249.0880.

**4.4.2. 9-Bromo-5,12-dihydro-5,6,11a-triazanaphthacen-11-one (16b).** White solid (68%); mp>260 °C; IR (KBr) $\nu$ 743, 1290, 1479, 1584, 1671, 3266 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$+$D_2O$) $\delta$ 5.13 (s, 2H), 6.95–7.00 (m, 2H), 7.21 (t, $J$=7.80 Hz, 1H), 7.25 (d, $J$=8.80 Hz, H-7), 7.29 (d, $J$=8.00 Hz, 1H), 7.74 (dd, $J$=2.40 Hz and $J$=8.80 Hz, H-8), 8.03 (d, $J$=2.40 Hz, H-10); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 42.67, 113.83, 113.99, 116.22, 119.18, 122.01, 126.37, 126.70, 128.18, 128.33, 135.16, 137.05, 146.79, 148.07, 160.12; MS (*m*/*z*) 327; HRMS (EI) $[M]^{+\bullet}$ ($C_{15}H_{10}N_3OBr$): calcd 327.0008; found 327.0350.

**4.4.3. 8-Chloro-5,12-dihydro-5,6,11a-triazanaphthacen-11-one (16c).** White solid (52%); mp>260 °C; IR (KBr) $\nu$ 775, 866, 1265, 1475, 1584, 1671, 3271 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$+$D_2O$) $\delta$ 5.12 (s, 2H), 6.95–7.00 (m, 2H), 7.17 (dd, $J$=2.30 Hz and $J$=8.60 Hz, H-9), 7.17–7.24 (m, 1H), 7.27–7.31 (m, 2H), 7.95 (d, $J$=8.60 Hz, H-10); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 42.76, 114.20, 116.49, 116.57, 122.45, 122.89, 123.35, 126.54, 128.58, 135.25, 139.31, 147.54, 150.32, 160.87; MS (*m*/*z*) 283; HRMS (EI) $[M]^{+\bullet}$ ($C_{15}H_{10}N_3OCl$): calcd 283.0512; found 283.0504.

**4.4.4. 3-(2-Aminobenzyl)-6-bromo-4-oxo-3,4-dihydroquinazoline-2-carbonitrile (17b).** Yellow solid (5%); mp=212 °C; IR (KBr) $\nu$ 852, 1386, 1625, 1666, 2237, 3032, 3358, 3431 $cm^{-1}$; $^1H$ NMR ($CDCl_3$+$D_2O$) $\delta$ 5.43 (s, 2H), 6.68 (d, $J$=8.00 Hz, 1H), 6.75–6.80 (m, 1H), 7.16 (m, 1H), 7.45–7.47 (m, 1H), 7.67 (d, $J$=8.80 Hz, H-8), 7.93 (dd, $J$=2.00 Hz and $J$=8.80 Hz, H-7), 8.47 (d, $J$=2.00 Hz, H-5); $^{13}C$ NMR ($CDCl_3$) $\delta$ 46.80, 112.14, 116.99, 118.16, 118.59, 123.58, 124.47, 129.98, 130.09, 130.42, 131.54, 131.78, 138.69, 145.04, 146.03, 159.94; MS (*m*/*z*) 354; HRMS (EI) $[M]^{+\bullet}$ ($C_{16}H_{11}N_4OBr$): calcd 354.0116; found 354.0110.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## References and notes


1. For reviews on quinazolinones and quinazolines see: (a) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153–10202; (b) Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 659–677; (c) Armarego, W. L. F. *Adv. Heterocycl. Chem.* **1997**, *24*, 1–62.
2. (a) Chen, J.-J.; Huang, H.-Y.; Duh, C.-Y.; Chen, I.-S. *J. Chin. Chem. Soc.* **2004**, *51*, 659–663; (b) Baruah, B.; Dasu, K.; Vaitilingam, B.; Mamnoor, P.; Venkata, P. P.; Rajagopal, S.; Yeleswarapu, K. R. *Bioorg. Med. Chem.* **2004**, *12*, 1991–1994; (c) Zhang, Y.; Zhang, Q.-H.; Wu, L.-J.; Tashiro, S.-I.; Onodera, S.; Ikejima, T. *J. Asian Nat. Prod. Res.* **2004**, *6*, 19–27; (d) Christopher, E.; Bedir, E.; Chuck, D.; Khan, I. A.; Okunji, C. O.; Schuster, B. M.; Iwu, M. M. *Helv. Chim. Acta* **2003**, *86*, 2914–2918; (e) Chang, H. W.; Kim, S. I.; Jung, H.; Jahng, Y. *Heterocycles* **2003**, *60*, 1359–1366; (f) Don, M.-J.; Lewis, D. F. V.; Wang, S.-Y.; Tsai, M. W.; Ueng, Y.-F. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2535–2538; (g) Yang, L.-M.; Chen, C.-F.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 465–468.
3. (a) Lee, E. S.; Park, J. G.; Kim, S. I.; Jahng, Y. *Heterocycles* **2006**, *68*, 1990–1998; (b) Ma, Z.; Hano, Y.; Nomura, T.; Chen, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1193–1196; (c) Cagir, A.; Eisenhauer, B. M.; Gao, R.; Thomas, S. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 6287–6299; (d) Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M.; Luotonin, A. *J. Am. Chem. Soc.* **2003**, *125*, 13628–13629; (e) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, *46*, 541–546.
4. (a) Bhattacharjee, A. K.; Hartell, M. G.; Nichols, D. A.; Hicks, R. P.; Stanton, B.; van Hamont, J. E.; Milhous, W. K. *Eur. J. Med. Chem.* **2004**, *39*, 59–67; (b) Sharma, V. M.; Prasanna, P.; Adi Seshu, K. V.; Renuka, B.; Laxman Rao, C. V.; Sunil Kumar, G.; Prasad Narasimhulu, C.; Aravind Babu, P.; Puranik, R. C.; Subramanyam, D.; Venkateswarlu, A.; Rajagopal, S.; Sunil Kumar, K. B.; Seshagiri Rao, C.; Rao Mamidi, N. V. S.; Deevi, D. S.; Ajaykumar, R.; Rajagopalan, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2303–2307; (c) Mitscher, L. A.; William, B. *Med. Res. Rev.* **1998**, *18*, 363–374.
5. (a) Mhaske, S.; Argade, N. P. *J. Org. Chem.* **2001**, *66*, 9038–9040; (b) Kamal, A.; Ramana, K. V.; Rao, M. V. *J. Org. Chem.* **2001**, *66*, 997–1001; (c) Jolivet-Fouchet, S.; Fabis, F.; Bovy, P.; Ochsenbein, P.; Rault, S. *Heterocycles* **1999**, *51*, 1257–1273; (d) Al-Shamma, A.; Drake, S.; Flynn, D. L.; Mitscher, L. A.; Park, Y. H.; Rao, G. S. R.; Simpson, A.; Swayze, J. K.; Veysoglu, T.; Wu, S. T. *J. Nat. Prod.* **1981**, *44*, 745–747.
6. Appel, R.; Janssen, H.; Siray, M.; Knoch, F. *Chem. Ber.* **1985**, *118*, 1632–1643.
7. Pereira, M.-F.; Alexandre, F. R.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* **2004**, *45*, 3097–3099.
8. For reviews on the chemistry of Appel's salt derivatives see: (a) Kim, K. *Sulfur Rep.* **1998**, *21*, 147–207; (b) Rees, C. W. *J. Heterocycl. Chem.* **1992**, *29*, 639–651.
9. Pereira, M.-F.; Picot, L.; Guillon, J.; Léger, J.-M.; Jarry, C.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* **2005**, *46*, 3445–3447.
10. (a) Cottenceau, G.; Besson, T.; Gautier, V.; Rees, C. W.; Pons, A. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 529–532; (b) Besson, T.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1659–1662; (c) Besson, T.; Emayan, K.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1995**, 1419–1420; (d) Besson, T.; Emayan, K.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2097–2102.
11. (a) Mohanta, P. K.; Kim, K. *Heterocycles* **2002**, *57*, 1471–1485; (b) Mohanta, P. K.; Kim, K. *Tetrahedron Lett.* **2002**, *43*, 3993–3996; (c) Lee, H.-S.; Chang, Y.-G.; Kim, K. *J. Heterocycl. Chem.* **1998**, *35*, 659–668.
12. Besson, T.; Rees, C. W.; Thiéry, V. *Synthesis* **1999**, 1345–1348.
13. Primot, A.; Baratte, B.; Gompel, M.; Borgne, A.; Liabeuf, S.; Romette, J. L.; Costantini, F.; Meijer, L. *Protein Expr. Purif.* **2000**, *20*, 394–404.
14. Borgne, A.; Meijer, L. *J. Biol. Chem.* **1996**, *271*, 27847–27854.
15. De Azevedo, W. F.; Leclerc, S.; Meijer, L.; Havlicek, L.; Strnad, M.; Kim, S. H. *Eur. J. Biochem.* **1997**, *243*, 518–526.
16. Schanche, J. S. *Mol. Divers.* **2003**, *7*, 293–300.