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[Continued on next page]

(54) Title: A FACILE PREPARATION OF 4-SUBSTITUTED QUINAZOLINES AND RELATED HETEROCYCLES

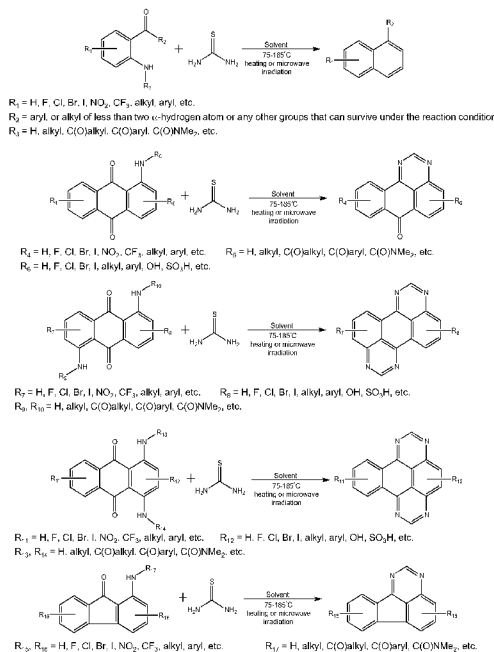


FIG. 4

(57) Abstract: A straightforward single step method for the preparation and/or production of substituted quinazolines is disclosed, wherein said quinazolines preferably contain one substituent at position 4, and may contain other functional groups at various positions, such as 5, 6, 7, and/or 8 of quinazolines. In addition, the extension of this new method leads to the formation of different type of heterocyclic aromatic compounds, that include but are not limited to perimidines, anthrapyrimidin-7-ones (also known as anthrapyrimidinones), anthra[1,9:5, 10]dipyrimidines (also known as quinazoline[5,4-ef]perimidines) and benzo[e]-pyrimido[4,5,6-gh]pyrimidines.

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## A FACILE PREPARATION OF 4-SUBSTITUTED QUINAZOLINES AND RELATED HETEROCYCLES

### CROSS-REFERENCE TO RELATED APPLICATIONS

5 [0001] This applications claims priority to U.S. Provisional Patent Application Serial No. 61/481804, filed May 3, 2011, which is hereby incorporated by reference for all purposes.

### FIELD

10 [0002] Disclosed herewith a unique, general and simple method to make, prepare and/or to produce substituted quinazolines that contain a substituent at position 4, and may or may not contain functional groups at other positions of the fused benzene ring within the quinazoline structure scaffold, such as at position 5, 6, 7, and/or 8 of quinazolines. The said functional groups at these positions may be individual groups, or fused aromatic rings.  
15 However, the substituent at position 4 may be an aromatic or a non-aromatic functional group. If the functional group at position 4 is an aromatic group, it may further contain a variety of substituents on it; whereas for those non-aromatic groups at position 4, the non-aromatic groups could be alkyl group or other common functional groups. Although the alkyl group may be any possible alkyl group, it should not carry more than two  $\alpha$ -hydrogens and  
20 preferably carries only one  $\alpha$ -hydrogen or does not carry  $\alpha$ -hydrogens at all.

### BACKGROUND

[0003] Quinazolines, being one type of nitrogenous heterocycles, have been identified with a variety type of biological activities, such as analgesic [1 (*Note: bracketed numerals used herein relate to listed references appearing below within the Detailed Description Of Illustrative Embodiments*)], antibacterial [2], antibiotic [1(b)], anticonvulsant [1(a),2(b),3],  
25 antidepressant [4], anti-inflammatory [1(a), 3, 5], anti-hypertensive [1(b), 3], antimalarial [2(a), 6], antineoplastic [2(a)], antitumoral [1(b), 7] as well as diuretic [1(b), 3], genotoxic [8], hypoglycemic [1(b)], narcotic [1(b)], sedative activities [1(b)] etc. Thus, the quinazoline derivatives have been applied as inhibitors for dihydrofolate reductase [2(a), 6], epidermal  
30 growth factor receptor [3, 7, 9], NADH-quinone reductase [10], TNF- $\alpha$  production [11], as well as T cell proliferation [11-12]. As a result, many pharmaceutical compounds containing quinazoline moiety have been widely applied for medicines.

[0004] For example, Alfuzosin is used in men to treat symptoms of an enlarged prostate [13], so-called benign prostatic hyperplasia [14]. Doxazosin, with structure and activity similar to Alfuzosin, is also used in men to treat the symptoms of an enlarged prostate [13-14]. Gefitinib is used to treat non-small cell lung cancer in people who have already been  
5 treated with other chemotherapy medications whereas whose conditions have not been improved or even become worse [9(a), 15]. Erlotinib, with a structure similar to Gefitinib, is also used to treat non-small cell lung cancer that has spread to the nearby tissues or to other parts of the body in patients who have already been treated with at least one other chemotherapy medication without obvious improvement [16]. Lapatinib is used to treat a  
10 certain type of advanced breast cancer in people who have already been treated with other chemotherapy medications [17].

[0005] In comparison, perimidine derivatives, with an extended aromatic system larger than quinazolines, have also been identified with a variety type of biological activities, such as antibacterial and antifungal activity [18], cytotoxic effect and in vivo immunosuppressant  
15 and immunostimulant activity [19], and have been applied as antagonists for nonpeptide corticotropin releasing factor (CRF) receptor [20]. In addition, perimidines usually absorb light of longer wavelength that could be stretched to the range of visible light and even to near-infrared range [21]. Thus, perimidines may appear in different colors, depending on the conjugated aromatic system as well as the functional groups they carry. As a result,  
20 perimidines have been developed as colorants, dyes and pigments [22].

[0006] Due to the wide applications of quinazolines as well as perimidines, a variety type of synthetic or preparative methods have been developed to make these type of heterocycles, according to the available starting materials and the structures of final products with different functional group distributions. Among these synthetic or preparative methods  
25 for quinazoline derivatives, a large portion of methods are focused on the introduction of the desired functional group into the existing quinazoline core-structure, which are not related to the current disclosure. In addition, even though there are still many synthetic methods for quinazoline derivatives that have a functional group attached to position 4 of quinazoline moiety through a heteroatom, such as oxygen, nitrogen, sulfur, etc., or with a functional  
30 group as simple as hydroxyl (OH), amino (NH<sub>2</sub>), or halogen (F, Cl, Br, I), these methods are in fact not related to the current disclosure either.

[0007] There is a need for a general, simple and direct method for the preparation and/or manufacturing of quinazoline derivatives that carry one substituent at position 4 of quinazoline ring via a carbon atom attachment, and may contain other functional groups at

the rest positions of quinazoline rings, except for position 2 of the quinazoline ring where no other functional group rather than hydrogen is attached. This direct method for the preparation of quinazoline derivatives also includes or is applicable to the preparation and/or manufacturing of even largely fused quinazoline derivatives that include perimidines, anthrapyrimidine-7-one, anthra[1,9:5,10]dipyrimidine and benzo[*e*]pyrimido[4,5,6-*gh*]pyrimidine when different 1-amino-9H-fluoren-9-ones, aminoanthraquinones are used as the starting materials. Likewise, only those methods for the preparation of perimidines, such as anthrapyrimidine-7-ones, anthra[1,9:5,10]dipyrimidines and benzo[*e*]pyrimido[4,5,6-*gh*]pyrimidines, which are closely related to the disclosed method will be compared below.

10 **[0008]** The preparation of quinazoline derivatives with a carbon-attached substituent at position 4 may be classified into several groups as described below, using 4-phenylquinazoline as in the following examples:

**[0009]** a) The preparation of 4-phenylquinazolines from an *N*-benzylideneaniline type of Schiff base that is formed from aniline and benzaldehyde, as shown in the reaction between *p*-chloro-(*α*-chlorobenzylidene)aniline and benzonitrile in 1,4-dichlorobenzene at 140°C in the presence of AlBr<sub>3</sub> that afforded 69% of 6-chloro-2,4-diphenylquinazoline [23], and the reaction between *N*-[*o*-(triphenylphosphoranylideneamino)benzylidene]-*p*-toluidine and *p*-nitrobenzaldehyde when refluxed in xylene for 12 hours that gave 70% of 6-methyl-4-*p*-nitrophenyl-2-phenylquinazoline [24]. The latter reaction would afford dihydroquinazolines as well if other benzaldehydes rather than *p*-nitrobenzaldehyde are used. In addition, the reaction between 3,4-diphenyl-1,2,4-oxadiazol-5(4H)-one and benzylideneaniline also afforded 2,4-diphenylquinazoline [25];

20 **[0010]** b) The preparation of 4-phenylquinazolines from amidobenzenes or benzonitriles, as shown in the reaction when *p*-chloropivalamidobenzene was dilithiated with *n*-BuLi followed by the addition of *o*-fluorobenzonitrile to give 57% of 2-*t*-butyl-6-chloro-4-*o*-fluorophenylquinazoline [26], and the treatment of *o*-aminobenzonitrile with phenylmagnesium halide from which the resulting intermediate 2-H<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>C(Ph)=N<sup>-</sup> then cyclized with carbonyl compounds (e.g., acid chlorides, anhydrides, formates) to give 4-phenyl-quinazolines [27]. Alternatively, the reaction between benzanilides and benzonitriles in the presence of PCl<sub>5</sub> and AlCl<sub>3</sub> in PhNO<sub>2</sub> at 120-150°C also afforded 2,4-  
30 diphenylquinazoline [28];

[0011] c) The reaction between benzenediazonium salt and benzonitrile, as shown in the reaction between *o*-benzylbenzenediazonium tetrafluoroborate and benzonitrile that gave 53% of 8-benzyl-2,4-diphenylquinazoline [29];

[0012] d) The conversion of benzo[*e*][1,4]diazepine derivatives into 4-phenyl-  
5 quinazolines, such as the refluxing of 3-hydroxy-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one in AcOH to give 35% of 4-phenyl-2-quinazolinecarbaldehyde [30], thermolysis of 7-chloro-3-(2-methylimidazol-1-yl)-5-phenyl-3H-1,4-benzodiazepin-2-amine in 50% H<sub>2</sub>SO<sub>4</sub> that afforded about 15% of 6-chloro-4-phenyl-2-quinazolinecarbaldehyde [31], thermolysis of 7-bromo-3-hydroxy-5-pyridin-2'-yl-3H-1,4-benzodiazepin-2(1H)-one at 220°C to give 6-  
10 bromo-4-pyridin-2'-yl-2-quinazolinecarbaldehyde [32], sublimation of 7-chloro-5-phenyl-1,3-dihydro-2,1,4-benzothiadiazepine 2,2,4-trioxide at 160°C under vacuum (at 10<sup>-3</sup> mmHg) to give 6-chloro-4-phenylquinazoline [33], acidic hydrolysis of 8-chloro-6-phenyl-3,4-dihydro-1,5-benzodiazocin-2-amine in refluxing methanolic hydrogen chloride for 2.5 hours to afford 53% of 2-*α*-aminoethyl-6-chloro-4-phenylquinazoline [34], treatment of 8-chloro-3-  
15 methyl-6-phenyl-3H-4,1,5-benzoxadiazocin-2(1H)-one with sodium methoxide for 20 hours to yield 50% of 2-acetyl-6-chloro-4-phenylquinazoline [35], oxidation of *N*-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepine-3-carboxamide with CrO<sub>3</sub> in AcOH to give 29% of *N*-methyl-6-nitro-4-phenyl-2-quinazolinecarboxamide [36], and hydrogenation of 8-chloro-6-phenyl-3H-4,1,5-benzoxadiazocin-2(1H)-one oxime over Raney-nickel to afford 50% of 6-chloro-2-  
20 hydroxymethyl-4-phenylquinazoline [37];

[0013] e) Thermolysis of 1,3,6-triphenyl-1,4-dihydro-1,2,4,5-tetrazine at 200°C to a mixture of three components that included 2,4-diphenylquinazoline [38];

[0014] f) The reaction between 3-phenylbenzo[*c*]isoxazole and 5-methoxy-3-phenyl-2,4-imidazolidinedione in refluxing dioxane containing TiCl<sub>4</sub> as catalyst to give 82% of 4,*N*-  
25 diphenyl-2-quinazolinecarboxamide [39];

[0015] g) Isomerization of 7-chloro-5-hydroxy-5-phenyl-1,2,3,5-tetrahydropyrrolo[1,2-*a*]-quinazolin-1-one into 2-*α*-carboxyethyl-6-chloro-4-phenylquinazoline in ~45% yield under basic condition [40];

[0016] h) The conversion of benzotriazene derivatives into 4-phenyl quinazolines, such  
30 as the transformation of 1,2-diaryl-2-(benzotriazol-1-yl)enamines prepared from lithiated (*α*-arylbenzotriazol-1-yl)methane and nitriles to afford 2,4-arylquinazolines, and the reaction between 2-(benzotriazol-1-yl)-1,2-diphenylethanone and formamide at 150°C to afford 50% of 2,4-diphenylquinazoline [41]; and

[0017] i) the treatment of 1-amino-4-methyl-9H-thioxanthen-9-one 10,10-dioxide with formic acid-formamide at 180°C for 3 hours to give a mixture of products from which 6-methyl-4-phenylquinazoline was isolated in low yield [42].

[0018] Although these known methods listed from a) to i) all lead to the formation of 4-phenylquinazolines, they are quite different from the presently disclosed method, because the cited methods mentioned above all afford 4-substituted quinazolines with an additional functional group at position 2 through a carbon-carbon attachment for which the removal of such group might prove difficult to accomplish.

[0019] Only the following several methods are of a kind of similarity to the presently disclosed method, to an extent, that all use 2-aminobenzophenone as the starting material. These similar synthetic methods include the reaction between 2-aminobenzophenone and ethyl carbamate and further treatment with phosphoryl trichloride [43], thermal reaction between 2-aminobenzophenone and formamide [44], the reaction between hydroxyglycine and 2-aminobenzophenones to give 1,2-dihydro-4-phenylquinazoline-2-carboxylic acids which is then converted into the corresponding quinazoline derivatives via air oxidation [45], and the treatment of 2-aminobenzophenone with urotropine and ethyl bromoacetate in alcohol to form a mixture of 4-phenylquinazoline and 4-phenyl-1,2-dihydroquinazoline [46].

[0020] For comparison, several methods have been developed for the preparation of aromatically-fused perimidine derivatives, including but not limited to anthrapyrimidine-7-ones, anthra[1,9:5,10]dipyrimidines and benzo[*e*]pyrimido-[4,5,6-*gh*]pyrimidines starting from aminoanthraquinones. Examples from such methods include the following:

[0021] a) a mixture of 1:2 ratio of 1-*N*-acetylaminoanthra-quinone and phenol when treated with ammonia gas at a pressure of 5 atm at 125-130°C afforded 2-methyl-1,9-anthrapyrimidine [47];

[0022] b) the thermal treatment of 1,5-diaminoanthraquinone-2-sulfonic acid with formamide followed by more than 10 times of 25% aqueous ammonia at 195-200°C afforded diamino-1,9-anthrapyrimidine [48];

[0023] c) the reaction of 5-amino-4'-benzoylamino-1,1'-anthrimidecarbazole with 5 equivalents (by weight) of formamide and 10 equivalents of phenol for several hours formed 4'-benzoylamino-5,10-pyrimidino-1,1'-anthrimidcarbazole [49];

[0024] d) treatment of 7.8 parts of *N,N*-dimethyl-*N'*-[anthraquinoyl(1)]-formamidinium chloride with 7.8 parts of ammonium acetate in 100 parts of glycol methyl monoether at 20°C for 30 minutes gave 5.2 parts of 1,9-anthrapyrimidine, which could also be prepared by the

treatment of 15.7 parts of *N,N*-dimethyl-*N'*-[anthraquinoyl-(1)]-formamidinium chloride with 14.4 parts of ammonium carbonate in 300 parts of methanol at 20°C for 30 minutes which gave 10.6 parts of 1,9-anthrapyrimidine [50];

[0025] e) treatment of 50 parts of 1-dimethylformamido-4-bromoanthraquinon-2-sulfonic acid with 25 parts (by weight) of an ammonium acetate in 800 parts of glycol monomethyl ether at 50°C for 4 hours afforded 28 parts of 4-bromo-anthrapyrimidin-2-sulfonic acid [51];

[0026] f) the reaction between 19.5 parts of 1,5-dihydroxy-4-propionylamino-8-aminoanthraquinone and 9.2 parts of dimethylformamide in 240 parts of chlorobenzene in the presence of 10.7 parts of thionyl chloride for 2 hours at 70°C, and the resulting product extracted with acetone was then treated with 30 parts of ammonium acetate in 250 parts of ethyleneglycol monomethyl ether at 75°C for 4 hours to afford 18.2 parts of 1,5-dihydroxy-4-propionylamino-8,10-anthrapyrimidine [52]; and

[0027] g) the reaction between 42.2 grams of 1,4-diamino-2,3-diphenoxy-anthraquinone and 31 grams of benzonitrile in 150 grams of trichlorobenzene in the presence of 34.4 grams of *p*-TsOH at 190°C for 5-6 hours afforded 46.6 grams of 6-amino-2-phenyl-4,5-diphenoxy-anthrapyrimidine [53].

### SUMMARY

[0028] The present disclosure provides a simple, direct and unique method to synthesize and/or produce quinazoline- and perimidine-based heterocycles. This disclosure covers the new method that involves the reaction between thiourea and a 2-aminobenzophenone or 2-aminoaryl aryl ketone or 2-aminoaryl alkyl ketone, in a solvent of high boiling point, and the composition of compounds prepared from this method.

[0029] The disclosed method for the preparation and/or production of substituted quinazolines results in quinazolines preferably containing one substituent at position 4, and may contain other functional groups at various positions, such as 5, 6, 7, and/or 8 of quinazolines. In addition, the extension of this new method leads to the formation of different type of heterocyclic aromatic compounds, that include but are not limited to perimidines, anthrapyrimidin-7-ones (also known as anthrapyrimidinones), anthra[1,9:5,10] dipyrimidines (also known as quinazoline[5,4-ef] perimidines) and benzo[e]-pyrimido[4,5,6-gh]pyrimidines.

[0030] The method includes a new chemical reaction between thiourea and a substituted 2-aminoaryl aryl ketone or a 2-aminoaryl alkyl ketone in a solvent of high boiling point. **FIG. 1** depicts the structure of starting material in this disclosure. The moiety of 2-aminoaryl may be phenyl, substituted phenyl, naphthyl, and other aromatic rings, either heterocyclic aromatic or not, with an amino group at the ortho position; and the amino group may be a primary or secondary amino group.

[0031] For the case of 2-aminophenyl aryl ketones where the 2-aminoaryl moiety is 2-aminophenyl, the 2-aminophenyl moiety may also contain other functional groups such as bromo, chloro, fluoro, methyl, methoxy, nitro, acetyl, etc. at one or up to four positions of the 2-aminophenyl ring. In addition, the aryl moiety, on the other side of 2-aminophenyl ketone, may be any aromatic ring or fused aromatic ring, either homogeneous aromatic ring (such as phenyl, naphthyl, etc) or heterocyclic ring (such as pyridyl, pyrimidyl, etc).

[0032] For the case of aliphatic 2-aminoaryl ketones, the 2-aminoaryl moiety may be any possible aromatic structures that are similar to the ones described in the case of 2-aminoaryl aryl ketones; however, the aliphatic moiety alone should not react with thiourea, solvent or amino group, and will not help the enolization of the adjacent carbonyl group, so that the alkyl moiety preferably carries no more than one  $\alpha$ -hydrogen atoms.

[0033] In addition, the reaction between thiourea and 1-amino-9H-fluoren-9-one, 1-aminoanthraquinone, 1,4-diaminoanthraquinone or 1,5-diaminoanthraquinone derivatives under the same condition affords perimidine derivatives, anthrapyrimidine-7-ones, anthra[1,9:5,10]dipyrimidines and benzo[*e*]pyrimido[4,5,6-*gh*]perimidines. These perimidine derivatives may contain other functional groups at the rest positions of the aromatic rings. The functional group may be alkyl, aryl, bromo, chloro, fluoro, methoxyl, acetyl, etc. Likewise, the amino group in this series of starting materials may be a primary amino group (-NH<sub>2</sub>) or secondary group (e.g., -NHCH<sub>3</sub>, -NHCOCH<sub>3</sub>, etc.).

[0034] Both quinazoline and perimidine derivatives have important applications in medicinal and pharmaceutical industries. In addition, the synthesized perimidine derivatives in this disclosure also have important applications in dye, colorant, and pigment industries.

### 30 **BRIEF DESCRIPTION OF THE DRAWINGS**

[0035] The features, nature, and advantages of the disclosed subject matter will become more apparent from the detailed description set forth below when taken in conjunction with the drawings, in which like references indicate like features and wherein:

[0036] FIG. 1 depicts the structure of the starting materials for the presently disclosed preparation of 4-substituted quinazolines and related heterocycles;

[0037] FIG. 2 shows the structures of quinazoline derivatives formed according to the teachings of the present disclosure;

5 [0038] FIG. 3 illustrates structures of perimidine and anthrapyrimidine series of heterocycles prepared according the disclosed subject matter;

[0039] FIG. 4 provides a reaction flow according to the present disclosure for the preparation of heterocycles; and

[0040] FIG. 5 displays gas chromatographic analysis results of a reaction mixture  
10 between thiourea and 2-aminobenzophenone in DMSO for analyzing reaction yield of the presently disclosed method.

[0041] **DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS**

[0042] **Composition:** The disclosed subject matter provides a new method to make  
15 quinazoline-based heterocycles as well as perimidine- or anthrapyrimidine-based heterocycles, starting from the reaction between thiourea and any ketone compounds containing a structural scaffold of 2-aminoaryl moiety, in a solvent of high boiling point.

[0043] For the quinazoline-based heterocycles, they contain a general structure as outlined in FIG. 2, in which R<sub>1</sub> may be halogens (F, Cl, Br or I), or alkyl, aryl, NO<sub>2</sub>, CF<sub>3</sub>, etc.  
20 at any position among the four possible sites (5, 6, 7, or 8), and when R<sub>1</sub> = aryl group, the aryl group may be attached to the quinazoline moiety with a single carbon-carbon bond at any position among the four binding sites, or fused to the quinazoline moiety. R<sub>18</sub> may be halogens (F, Cl, Br or I), or alkyl, aryl, CO<sub>2</sub>H, etc. that are attached to any positions among the five possible binding sites (from 2' to 6'). Likewise, when R<sub>18</sub> = aryl, the aryl group may  
25 be attached to the 4-phenyl ring either through a single carbon-carbon attachment to any carbon atom from 2' to 6', or fused to the 4-phenyl ring. R<sub>2</sub> should be an alkyl group containing less than two -hydrogen atoms so that the alkyl group will not enolize with the adjacent carbonyl group before the ketone starting material is transformed into quinazoline. In addition, R<sub>2</sub> may also be any other functional groups that will not react with thiourea or  
30 amino group and can survive under the reaction condition.

[0044] For the perimidine- or anthrapyrimidine-based heterocycles, four general structures, i.e., perimidines, anthrapyrimidin-7-ones, anthra[1,9:5,10]dipyrimidines, and benzo[e]pyrimido[4,5,6-gh]pyrimidines, are shown in FIG. 3, in which R<sub>4</sub>, R<sub>7</sub>, R<sub>11</sub>, R<sub>15</sub>, and R<sub>16</sub> may be halogens (F, Cl, Br or I), or alkyl, aryl, OH, etc. at any position among the

possible sites, and R<sub>6</sub>, R<sub>8</sub> and R<sub>12</sub> may be halogens (F, Cl, Br or I), alkyl, aryl, OH, SO<sub>3</sub>H, etc. at any position among the possible sites.

[0045] The disclosed subject matter provides a unique and simple method to prepare the heterocycles described above, involving a reaction between thiourea and an aryl ketone with an *ortho* amino group on the aryl ring that is heated in a solvent of high boiling point, as shown in FIG. 4. The solvents of high boiling points may be water (b.p. 100°C), *N,N*-dimethylformamide (DMF, b.p. 153°C), dimethyl sulfoxide (DMSO, b.p. 189°C), ethylene glycol (b.p. 195-198°C), 2-methoxyethanol (b.p. 124-125°C), diethylene glycol monomethyl ether (b.p. 190-194°C), *p*-dichlorobenzene (b.p. 173°C), etc.

[0046] Among these possible solvents, DMSO would be the preferred solvent. The reaction may be carried out at a temperature in the range from 75°C to 185°C, and preferably in the range from 110°C to 165°C. The high reaction temperature for this reaction may be maintained through heating via heating mantle, oil bath, hot plate or even with hot air or other heat transmitting media, or via heating with microwave irradiation. A comparable yield of the heterocycle may be obtained under either reaction conditions, i.e., via heating or microwave irradiation, although the reaction carried out under microwave irradiation is more suitable for a relatively small-scale reaction (up to 20 mL).

[0047] Under the optimized reaction condition, the disclosed reaction usually affords quinazoline of yield up to 100%, according to GC/MS analysis, as shown in FIG. 5. Usually, a single product is formed. Therefore, the isolation of product is very simple and straightforward, where the formed product may crystallize directly from the reaction solvent when the reaction mixture is cooled down to room temperature. However, if no crystal forms, the product may be isolated with conventional methods.

[0048] In addition, the extension of this method starting from aminoanthraquinones under conditions similar to the ones to form quinazolines will form even enlarged aromatic heterocycles, that include perimidines, such as anthrapyrimidine-7-ones, anthra[1,9:5,10]dipyrimidines and benzo[*e*]pyrimido[4,5,6-*gh*]pyrimidines.

#### **EXPERIMENTS OF THE DISCLOSURE**

[0049] The structures of the presently disclosed facile preparation of 4-substituted quinazolines and related heterocycles are evidenced by the following examples:

[0050] ***Example 1:*** To a 20 mL microwave reaction vial with a micro magnetic stir bar, were added 0.460 g of 2-aminobenzophenone, 0.355 g of thiourea and 3.5 mL of DMSO.

Then, the vial was sealed and heated with microwave at 155°C for 5 hours. GC/MS analysis indicated that all 2-aminobenzophenone has been transformed into 4-phenyl-quinazoline as a single product. The reaction mixture was added to 25 mL of EtOAc and washed with water for three times and dried. The product was loaded on silica gel for column chromatography with hexane/EtOAc (5:1) as the eluent, affording an isolated yield of 4-phenyl-quinazoline greater than 85%.

[0051] **Example 2:** To a 25 mL round-bottomed flask were added 0.847 g of 2-aminobenzophenone, 0.658 g of thiourea and 6.0 mL of DMSO, and the mixture was heated at 155°C for 5 hours. Work out of the reaction mixture by means of a method similar to Example 1 afforded 4-phenyl-quinazoline with a yield comparable to the reaction condition performed under microwave irradiation.

[0052] **Example 3:** To a one-drum vial were added 0.077 g of 2-aminobenzophenone, 0.060 g of thiourea and 0.35 mL of DMSO. Then the capped vial was left on hot-plate at 155°C for 5 hours, GC/MS analysis indicated that all 2-aminobenzophenone has been consumed and only 4-phenyl-quinazoline was identified as the product at 8.35 minutes when the GC was programmed from 100°C (1 min) to 250°C (2 min) at a speed of 20°C/min to raise the oven temperatures.

[0053] **Example 4:** To a 20 mL microwave reaction vial with a micro magnetic stir bar, were added 0.297 g of 2-amino-2',5-dichlorobenzophenone, 0.170 g of thiourea and 3 mL of DMSO. Then the vial was sealed and heated with microwave at 140°C for 10 hours. The reaction mixture was worked out by dissolving in 25 mL of EtOAc and washed with water. As the reaction was heated at a lower temperature and worked out before its completion, the product was contaminated with the starting material so that silica gel column chromatography was used to purify the product, with hexane/EtOAc (5:1) as the eluent to afford 0.155 g of 2',6-dichloro-4-phenyl-quinazoline, in a yield of 50.5%.

[0054] The same reaction with 0.296 g of 2-amino-2',5-dichlorobenzophenone and 0.170 g of thiourea at 140°C for 20 hours afforded 0.216 g of 2',6-dichloro-4-phenyl-quinazoline, after similar purification method, in a yield of 70.6%.

[0055] **Example 5:** To a 20 mL microwave reaction vial with a micro magnetic stir bar, were added 0.297 g of 2-amino-5-nitrobenzophenone, 0.186 g of thiourea and 3.0 mL of DMSO. Then the vial was sealed and heated with microwave at 140°C for 20 hours. Two layers of liquid formed with brown liquid on the top and a dark brown gel like layer at the bottom. The reaction mixture was extracted with EtOAc and purified on column

chromatography using hexane/EtOAc (5:1 to 4:1) as eluent, and 0.122 g of 4-phenyl-6-nitro-quinazoline was obtained, in a yield of 39.7%.

[0056] **Example 6:** To a 20 mL microwave reaction vial with a micro magnetic stir bar, were added 0.300 g of 1-aminoanthra-quinone, 0.207 g of thiourea and 3 mL of DMSO. Then  
5 the vial was sealed and heated with microwave at 140°C for 20 hours. A dark brown gel like mixture was obtained which was purified in a similar fashion with hexane/EtOAc (5:1 to 1:1) as the eluent, and 0.103 g of anthrapyrimidine was obtained, in a yield of 33.0%.

[0057] **Example 7:** To a 20 mL microwave reaction vial with a micro magnetic stir bar, were added 0.284 g of 2-amino-4-methyl-benzophenone, 0.208 g of thiourea and 3 mL of  
10 DMSO. Then the vial was sealed and heated with microwave at 140°C for 20 hours to form an orange liquid. The reaction mixture was treated in a similar method via column chromatography with hexane/EtOAc (6:1) as eluent to afford 0.293 g of 4-phenyl-7-methyl-quinazoline, in a yield of 99.0%.

[0058] Although the present disclosure is described with reference to specific  
15 embodiments, one skilled in the art could apply the principles discussed herein to other areas and/or embodiments without undue experimentation.

[0059] The subject matter of the present disclosure is well adapted to attain the ends and advantages mentioned as well as those that are inherent therein. The particular embodiments disclosed above are illustrative only, as the present disclosure may be modified and practiced  
20 in different but equivalent manners apparent to those skilled in the art having the benefit of the teachings herein. Furthermore, no limitations based on the details of construction or design herein shown are intended, other than as described in the claims below. It is therefore evident that the particular illustrative embodiments disclosed above may be altered or modified, and all such variations are considered within the scope and spirit of the present  
25 disclosure.

[0060] **REFERENCES:** The following references are illustrative for highlighting the inventive subject matter of the present disclosure, wherein associated numerals relate to citation numbers discussed in the above **Background** section.

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5

**WHAT IS CLAIMED IS:**

1. A method for forming a 4-substituted quinazoline derivative, comprising the steps of:

providing thiourea as a reagent;

5 providing an organic compound comprising a 2-aminobenzoyl or 2-aminoarylcarbonyl moiety as a starting material from a set consisting essentially of 2-aminobenzophenone, 2-aminoaryl aryl ketone and 2-aminoaryl alkyl ketone, said starting material comprising a 2-aminoarylcarbonyl moiety;

mixing said thiourea and said organic compound;

10 reacting said mixture in a solvent of high boiling point from a set consisting essentially of water, DMF, DMSO, ethylene glycol, 2-methoxyethanol, diethylene glycol monoethyl ether, and p-dichlorobenzene at a temperature ranging from approximately 75°C to approximately 185°C to yield a quinazoline comprising at least one substituent at position 4.

15 2. The method of Claim 1, further comprising the step of reacting said mixture to yield a quinazoline wherein at least one and up to four functional groups attach to said 2-aminoaryl moiety of said starting material, and further wherein said functional groups comprise either an aromatic group or a non-aromatic group.

20 3. The method of Claim 2, wherein when one of said functional groups on said 2-aminoaryl moiety of said starting material comprises an aromatic group, said aromatic group further comprising either an individual attachment to said 2-aminoaryl moiety or a fusing attachment to said 2-aminoaryl moiety, said individual attachment comprising a single carbon-carbon bond.

25 4. The method of Claim 1, wherein said starting material comprises a 2-aminoaryl aryl ketone where said aryl moiety of said 2-aminoaryl aryl ketone comprises up to five functional groups, said functional groups comprising either aromatic groups or non-aromatic groups.

30 5. The method of Claim 4, wherein when one of said functional groups on said aryl moiety comprises an aromatic group, said aromatic group can be either attached to said aryl moiety via an individual attachment comprising a single carbon-carbon bond or attached to said aryl moiety via a fusing attachment to said aryl moiety.

6. The method of Claim 1, wherein said starting material comprises a 2-aminoaryl alkyl ketone, with or without additional functional groups on said 2-aminoaryl moiety.

7. The method of Claim 6, wherein said at least one and up to four functional groups comprise an attachment to said 2-aminoaryl moiety of said starting materials, and said  
5 functional groups comprise either aromatic groups or non-aromatic groups.

8. The method of claim 7, wherein if one of said functional groups on said 2-aminoaryl moiety of said starting material comprises an aromatic group, said aromatic group comprising either an individual attachment to said 2-aminoaryl moiety via a single carbon-carbon bond or a fusing attachment to said 2-aminoaryl moiety.

9. The method of claim 6, wherein said alkyl moiety of said starting material comprises not more than two  $\alpha$ -hydrogens, thereby preventing tautomerization of said alkyl moiety with an adjacent carbonyl group for forming an enol and avoiding aldol condensation and resultantly simplifying said steps.

10. The method of Claim 1, wherein said starting material comprises a 2-aminobenzoyl or 2-aminoarylcarbonyl moiety, and further comprises said functional groups  
15 directly attach to the carbonyl of said 2-aminobenzoyl or 2-aminoarylcarbonyl of said starting material other than said 2-aminoaryl moiety or alkyl moiety.

11. The method of Claim 1, wherein said starting material further comprises a 1-amino-9H-fluoren-9-ones, said 1-amino-9H-fluoren-ones optionally comprising functional  
20 groups on either benzene ring within said 1-amino-9H-fluoren-9-ones.

12. The method of Claim 1, wherein said amino group on said starting material consists essentially of an amino group from a group consisting essentially of primary amino group  $\text{NH}_2$  and secondary amino groups such as  $\text{NHCH}_3$ ,  $\text{NHCOCH}_3$ .

13. The method of Claim 1, wherein said starting material further comprises an  
25 anthraquinone, said anthraquinone comprising at least one amino group at position 1 and optionally at least one additional functional group at other positions.

14. The method of Claim 13, wherein said anthraquinone further comprises at least two amino groups, wherein one of said at least two amino groups is located at position 1 and

another of said at least amino groups attaches at either position 4 or position 5 of core structure of said anthraquinone.

15. A composition comprising a quinazoline derivative, said quinazoline derivative comprising:

5 a functional group at position 4 of a quinazoline core structure of said quinazoline derivative associated via a carbon-carbon attachment;

wherein no additional functional group rather than hydrogen appears at position 2 of said quinazoline core structure; and

10 further wherein additional functional groups may appear at other positions of said quinazoline core structure;

wherein said quinazoline is formed by the method comprising the steps of:

providing thiourea as a reagent;

15 providing an organic compound comprising a 2-aminobenzoyl or 2-aminoarylcarbonyl moiety as a starting material from a group consisting essentially of 2-aminobenzophenone, 2-aminoaryl aryl ketone and 2-aminoaryl alkyl ketone, said starting material comprising a 2-aminoaryl moiety;

mixing said thiourea and said organic compound;

20 reacting said mixture in a solvent of high boiling point at a temperature ranging from approximately 75°C to approximately 185°C to yield a quinazoline comprising at least one substituent at position 4.

16. The composition of Claim 15, further comprising a phenyl group at position 4 of said quinazoline core structure, wherein said phenyl group optionally comprises additional functional groups associated with said phenyl group by either individual attachment of a single carbon-carbon bond or a fusing attachment to said phenyl ring.

25 17. The composition of Claim 16, wherein said quinazoline derivative optionally comprises an additional aromatic group on said quinazoline core structure rather than position 2 and 4, said additional aromatic group attaching to said quinazoline core structure by an individual attachment of a single carbon-carbon bond or a fusing attachment to said quinazoline ring.

18. The composition of Claim 16, comprising an aromatic ring of perimidines, anthrapyrimidin-7-ones, or anthrax[1,9:5,10]pyrimidines or benzo[e]pyrimido[4,5,6-*gh*]pyrimidines, with optionally additional functional groups.

19. The composition of Claim 18, wherein additional functional groups attach to said  
5 perimidines, anthrapyrimidin-7-ones, or anthrax[1,9:5,10]pyrimidines or  
benzo[e]pyrimido[4,5,6-*gh*]pyrimidines core structures, said additional functional groups  
optionally comprising aromatic groups and non-aromatic groups.

20. The composition in Claim 19, wherein said additional functional groups comprise  
aromatic groups, said aromatic groups optionally comprising further functional groups  
10 associated with said aromatic groups.

$R_1, R_4, R_7, R_{11}, R_{15}, R_{16} = H, F, Cl, Br, I, NO_2, CF_3, alkyl, aryl, etc.$

$R_2 = aryl$ , alkyl of less than two  $\alpha$ -hydrogen atom or any other groups that can survive under the reaction condition

$R_3, R_5, R_9, R_{10}, R_{13}, R_{14}, R_{17} = H, alkyl, C(O)alkyl, C(O)aryl, C(O)NMe_2, etc.$

$R_6, R_8, R_{12} = H, F, Cl, Br, I, alkyl, aryl, OH, SO_3H, etc.$

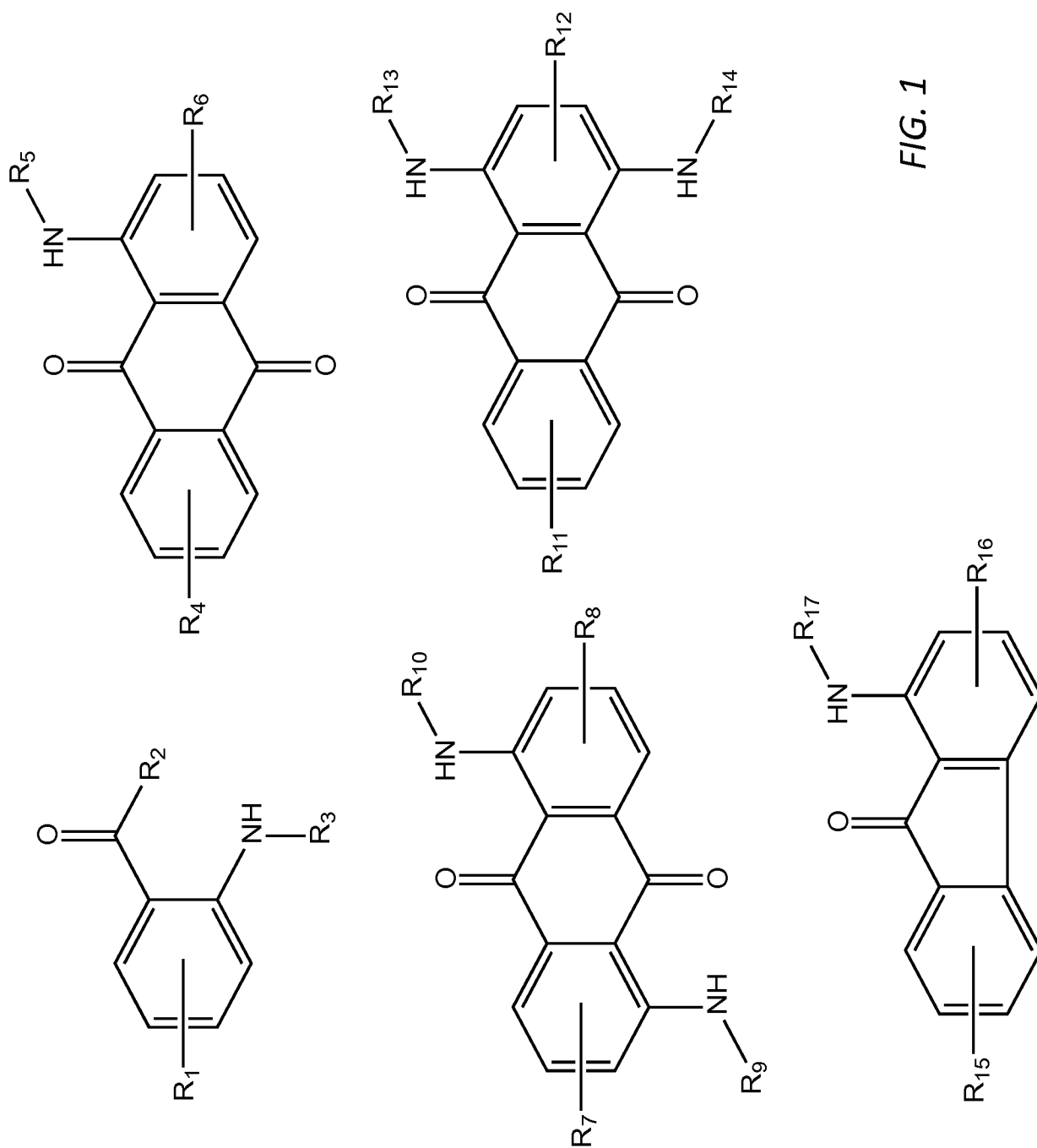


FIG. 1

$R_1, R_{18} = H, F, Cl, Br, I, NO_2,$   
 $CF_3, alkyl, aryl, etc.$

$R_2 = aryl, alkyl$  of less than  
two  $\alpha$ -hydrogen atom or any  
other groups that can survive  
under the reaction condition.

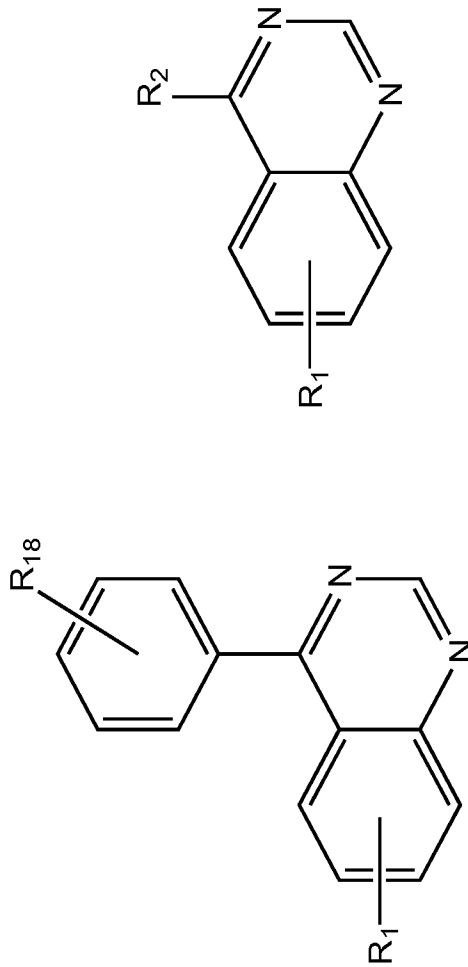
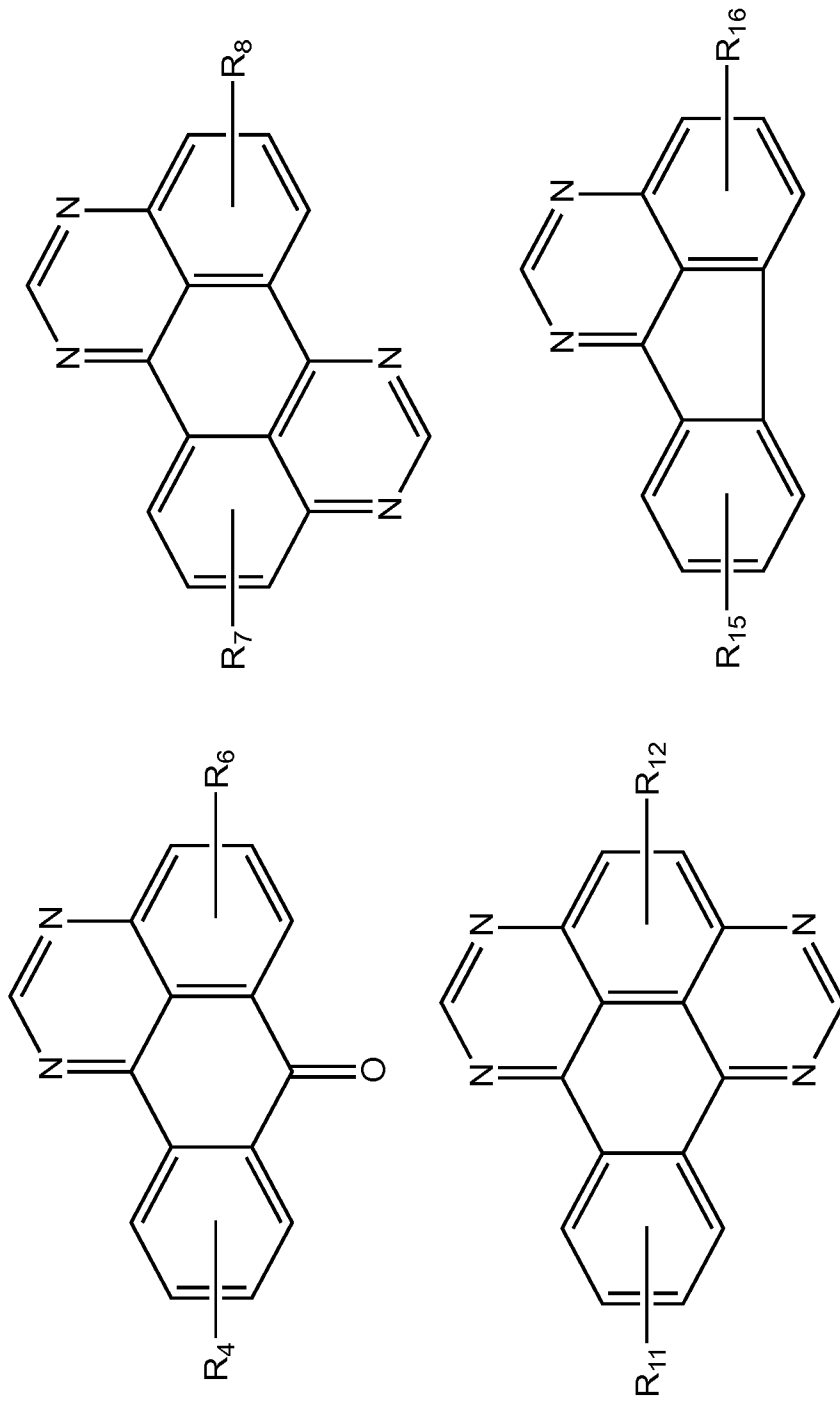


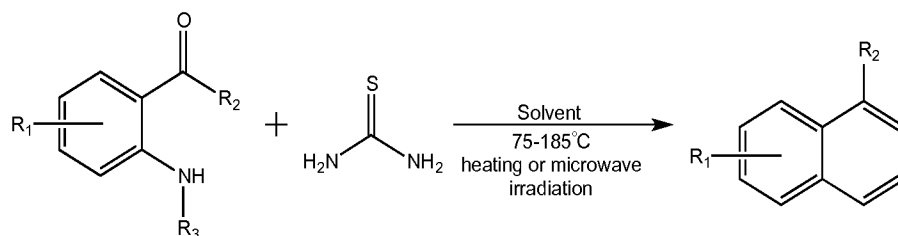
FIG. 2



R<sub>4</sub>, R<sub>7</sub>, R<sub>11</sub>, R<sub>15</sub>, R<sub>16</sub> = H, F, Cl, Br, I, NO<sub>2</sub>, CF<sub>3</sub>, alkyl, aryl, etc.

R<sub>6</sub>, R<sub>8</sub>, R<sub>12</sub> = H, F, Cl, Br, I, alkyl, aryl, OH, SO<sub>3</sub>H, etc.

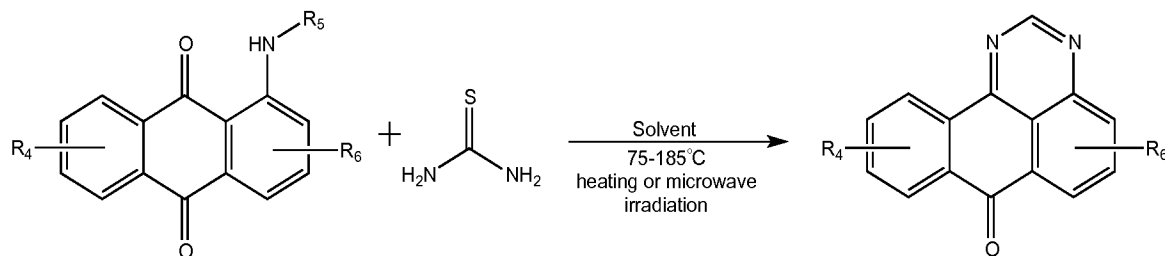
FIG. 3



$R_1 = \text{H, F, Cl, Br, I, NO}_2, \text{CF}_3, \text{alkyl, aryl, etc.}$

$R_2 = \text{aryl, or alkyl of less than two } \alpha\text{-hydrogen atom or any other groups that can survive under the reaction condition}$

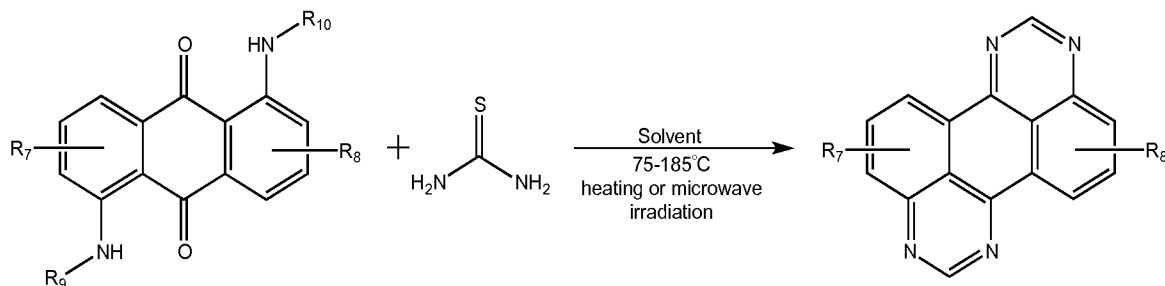
$R_3 = \text{H, alkyl, C(O)alkyl, C(O)aryl, C(O)NMe}_2, \text{etc.}$



$R_4 = \text{H, F, Cl, Br, I, NO}_2, \text{CF}_3, \text{alkyl, aryl, etc.}$

$R_5 = \text{H, alkyl, C(O)alkyl, C(O)aryl, C(O)NMe}_2, \text{etc.}$

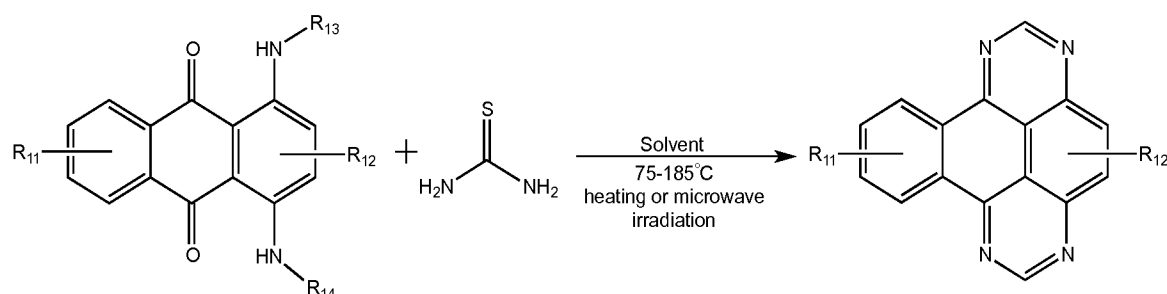
$R_6 = \text{H, F, Cl, Br, I, alkyl, aryl, OH, SO}_3\text{H, etc.}$



$R_7 = \text{H, F, Cl, Br, I, NO}_2, \text{CF}_3, \text{alkyl, aryl, etc.}$

$R_8 = \text{H, F, Cl, Br, I, alkyl, aryl, OH, SO}_3\text{H, etc.}$

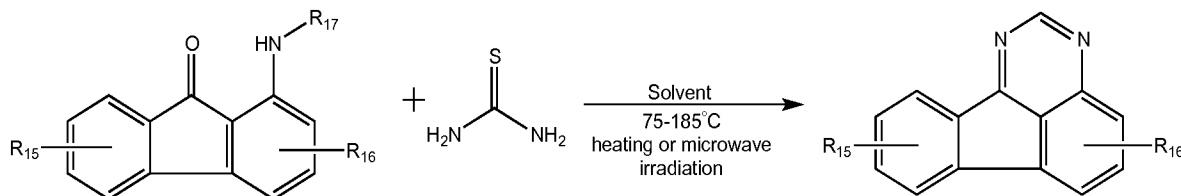
$R_9, R_{10} = \text{H, alkyl, C(O)alkyl, C(O)aryl, C(O)NMe}_2, \text{etc.}$



$R_{11} = \text{H, F, Cl, Br, I, NO}_2, \text{CF}_3, \text{alkyl, aryl, etc.}$

$R_{12} = \text{H, F, Cl, Br, I, alkyl, aryl, OH, SO}_3\text{H, etc.}$

$R_{13}, R_{14} = \text{H, alkyl, C(O)alkyl, C(O)aryl, C(O)NMe}_2, \text{etc.}$



$R_{15}, R_{16} = \text{H, F, Cl, Br, I, NO}_2, \text{CF}_3, \text{alkyl, aryl, etc.}$

$R_{17} = \text{H, alkyl, C(O)alkyl, C(O)aryl, C(O)NMe}_2, \text{etc.}$

FIG. 4

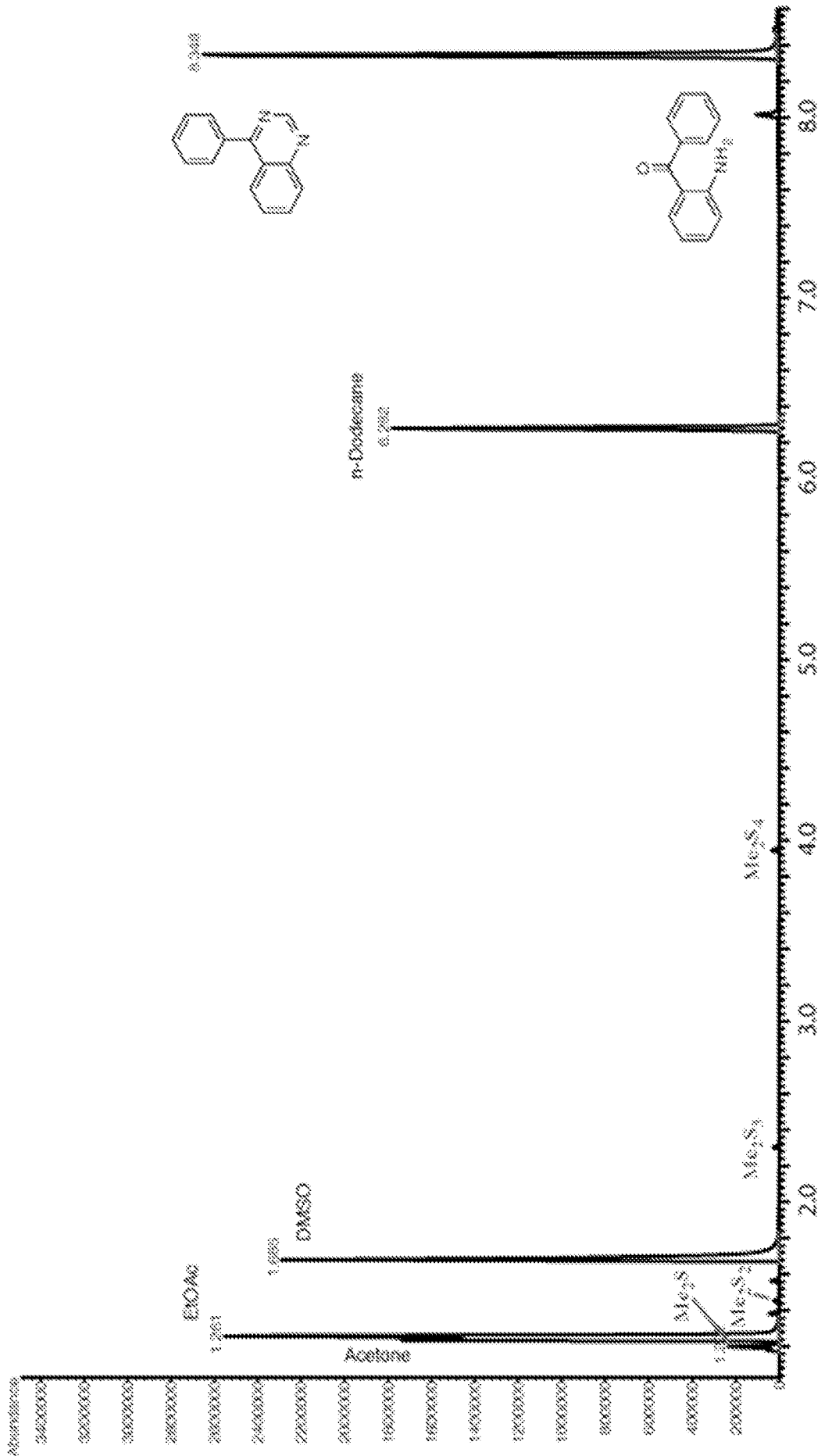


FIG. 5