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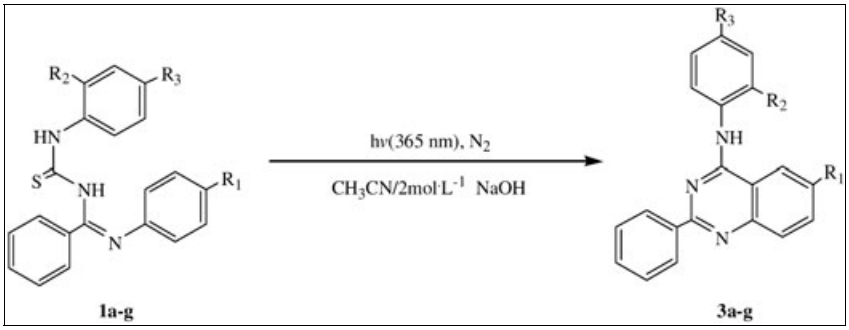

A series of quinazoline derivatives were synthesized via the cyclization of *N*, *N*′–disubstituted thiourea derivatives in the mixed solvent of acetontrile and aqueous NaOH by ultraviolet light irradiation. All the compounds are characterized by IR, ^{1}HNMR, ^{13}CNMR, MS, and element analysis. The absolute configurations of **3a** was determined by X-ray crystallography.

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INTRODUCTION

The synthesis of new heterocyclic compounds has been an important subject due to their wide applicability. Among a large variety of heterocyclic compounds, heterocycles containing quinazoline have attracted great interest in recent years because of their important biological activities. First, they can be used as putative irreversible inhibitors of the epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER-2) in human cancers[1–4], Second, they also can be used as potential anti-inflammatory [5], antifungicidal [6], antibacterial [7], antihypertensive [8] reagents, and α1-adrenoceptor antagonists [9]. In addition, some of them are known as photo-affinity reagents for investigating protein identification, structure, localization, and active-site determination [10]. Accordingly, the development of efficient synthetic strategies for the construction of this molecular architecture is of considerable importance from the standpoint of the pharmaceutical and organic chemistry.

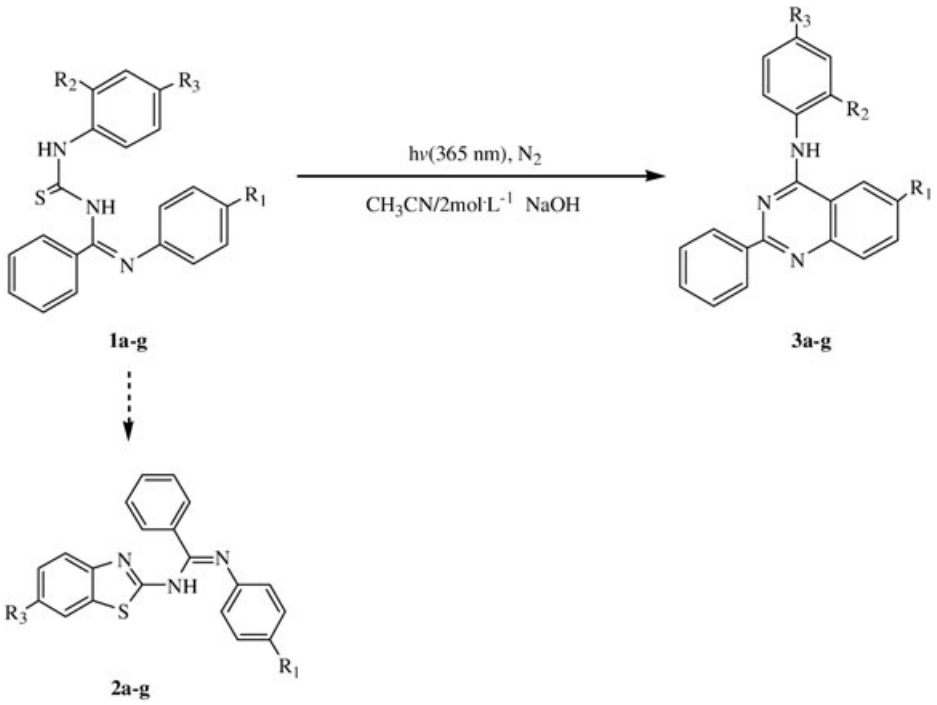
Many quinazoline derivatives have been synthesized using various methods, such as solid-phase [11], microwaves [12], cyclization [13], oxidation [14], and One-pot synthesis [15] with different starting materials, such as anthranilic acid, 2-aminobenzonitrile, 2-nitrobenzoic acid, anthranilamide, and so on. Although quninazoline derivatives have been synthesized successfully, photochemical method utilized for the synthesis of quinazoline derivatives has not been reported. We hereby report preliminary results on the photocyclization of substituted thiourea to quinazoline derivatives in basic conditions.

RESULTS AND DISCUSSION

Previously the synthesis was reported of 1,3–diarylthiourea or substituted 1,2,4-triazole-3-thiones which, under 254 nm ultraviolet light irriadiation for certain hours in alchol or mixed solution of CH_3CN and aqueous NaOH, underwent photosubstitution to gave benzothiazole ring system and triazolobenzothiazines systems, respectively [16–18]. It is indicated that both *ortho*-halogen substituent and function group of thiourea are all necessary for the synthesis of benzo-heterocycle compounds by photochemistry. However, irriadiation of compound **1a-g** under a high-pressure mercury lamp (365 nm) in the mixed solution of CH_3CN and aqueous NaOH at room tempture gave not the expected products **2a-g** but the novel product of 4-Arylamino-2-phenyl-6-substituted-quinazoline **3a-g** with moderate yield. The synthetic route was shown in Scheme 1 and the results are summarized in Table 1.

N, *N*′–disubstituted thiourea **1a-g,** the starting materials, were prepared by the literature procedure [19], All the newly synthesized compounds **3a-g** were characterized

Scheme 1



by ^{1}HNMR, ^{13}C NMR, and MS (see Experimental section).

In the ^{1}HNMR spectra, the characteristic chemical shift of the amino protons of **3a–g** were found at δ = 7.29–8.15 as a broad singlet. The aromatic protons were found at δ = 7.00–9.00 as multiplet. IR spectra of all newly synthesized compounds **3a–g**, contain characteristic bands attributed to the NH stretching at about 3434 cm^{-1} and the –C═N stretching at about 1526 cm^{-1}, which are the structural characteristics of this type of compounds. The element analysis and MS of **3a–g** agreed with the molecular formula of these compounds.

Crystal structure of the compound 3a. The molecular structure of **3a** was confirmed by X-ray crystallography. Single crystals of **3a** were obtained by slow evaporation of the compound **3a** in acetonitrile at ambient temperature. The molecular structure of **3a** is shown in Figure 1 and selected bond lengths and bond angles are listed in Table 2. The X-ray structure analysis indicates that **3a** consists of two phenyl rings and one quinazoline ring. These rings do not share a common plane. The phenyl ring and the 2-chlorophenyl ring make the dihedral angles with 6-methoxyquinazoline plane are 5.3(2)° and 39.8(3)°, respectively. Furthermore, the quinazoline molecule is nearly coplanar with the dihedral angles between the phenyl planes and the pyrimidine plane is 0.7(2)° forming a bigger conjugated system. The bond lengths and bond angles in the structure of **3a** are in the usual ranges.

EXPERIMENTAL

The solvent and all reagents used in this study were purchased from commercial suppliers and were used as received. Melting point was taken on a Yanagimoto MP-500 apparatus and uncorrected. IR spectra were measured on a BIO-RAD FTS 3000 spectrometer using KBr disks. The ^{1}HNMR spectra and ^{13}CNMR spectra were recorded on a Bruker AVANVE 300 MHz nuclear magnetic resonance spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. EI-MS spectra were measured on a Waters Xevo-TQMS(HPLC-MS). The elemental analysis was performed on FLASH EA1112 elemental analyzer.

The X-ray data were collected at ambient temperature by means of a CCD area detector, using graphite monochromated MoKa radiation. The structure was solved by direct methods using SHELXL-97 program and refined by full-matrix least-squares

Table 1

Photoproducts of 4-arylamino-2-phenyl-6-substituted-quinazoline **3a-g**.

Product	R_1	R_2	R_3	Time[a]	Yield (%)[b]	MP (°C)
3a	OCH_3	Cl	H	7	49	159–161
3b	CH_3	H	CH_3	5	44	141–142
3c	CH_3	Cl	H	4.5	39	142–144
3d	H	Cl	H	5	44	141–142
3e	Cl	Cl	H	6	44	193–195
3f	Cl	H	CH_3	4	45	164–166
3g	H	H	H	5.5	42	138–140

[a]Time in hours.
[b]Pure isolated yields of products.

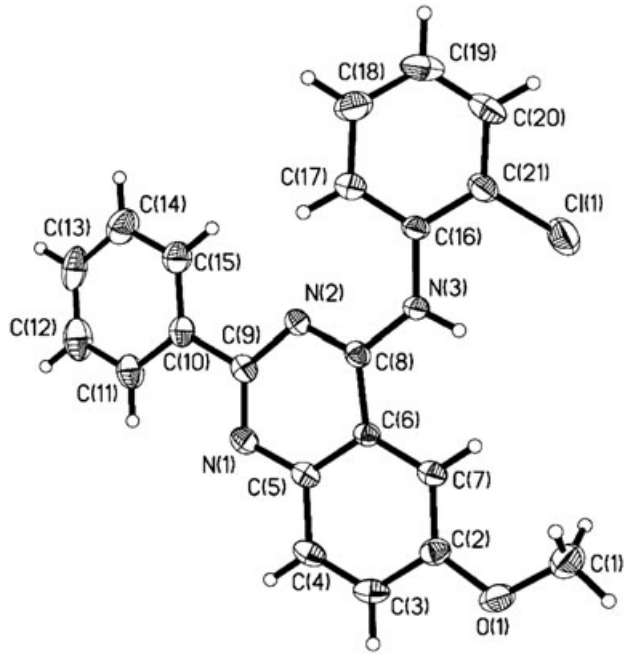


Figure 1. The molecular structure of **3a**.

on F^2. Minimum and maximum final electron density was 0.262 and 0.192 eÅ^{-3}. All nonhydrogen atoms were refined anisotropically, and hydrogen atoms were added according to theoretical modes. The final cycle of refinement gave $R = 0.0472$, $wR = 0.0861$ (The weighting scheme was $w = 1/[s^2(F_o^2)+(0.0357P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$). Plots were produced with the XP program. Selected crystal data and refinement results are listed in Table 3.

Syntheses. ***General procedure for the preparation of the 4-arylamino-2- phenyl-6-substituted-quinazoline 3a-g.*** To 1,3-disubstituted thiourea (0.5 mmol) in a quartz tube was added CH_3CN (300 mL) and aqueous NaOH (20 mL, 2 mol L^{-1}). The mixture, deaerated by nitrogen purging for 1 h, was stirred and irradiated under a high-pressure mercury lamp(365 nm) and for given hours. After completion of the reaction (checked by TLC), the reaction mixture was seperated, the organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure, the crude reaction mixture was purified by column chromatography over silica gel using chloroform as eluent to give the desired product.

4-(2-Chlorophenylamino)-6-methoxy-2-phenylquinazoline (3a). IR (KBr): 3434, 1526, 1358 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ 3.98 (s, 3H, OCH_3), 7.08-7.11 (m, 1H, ArH), 7.14 (d, J = 2.5 Hz, 1H, ArH), 7.44-7.54 (m, 6H, ArH), 7.94 (s, 1H, ArH), 7.96 (s, 1H, NH), 8.52-8.54 (m, 2H, ArH), 9.01 (dd, J_1 = 1.0 Hz, J_2 = 7.0 Hz, 1H, ArH). ^{13}CNMR ($CDCl_3$): δ 55.69, 99.72, 114.65, 121.94, 123.28, 123.63, 124.12, 127.66, 128.16, 128.43, 129.10, 129.99, 131.04, 135.60, 138.64, 146.66, 155.99, 157.93, 158.29. MS 362(m/z): 362 (M^+ + 1). Anal. Calc. for $C_{21}H_{16}ClN_3O$: C, 69.71; H, 4.46; N, 11.61%. Found: C, 69.79; H, 4.52; N, 11.58%.

6-Methyl-4-(4-methylphenylamino)-2-phenylquinazoline (3b). IR (KBr): 3439, 1521, 1359 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 7.25 (dd, J_1 = 1.0 Hz, J_2 = 8.0 Hz, 2H, ArH), 7.34 (s, 1H, NH), 7.44-7.50 (m, 3H, ArH), 7.56-7.59 (m, 2H, ArH), 7.76 (dd, J_1 = 2.0 Hz, J_2 = 6.5 Hz, 2H, ArH), 7.86 (d, J = 7.5 Hz, 1H, ArH), 8.51-8.53 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 20.94, 21.78, 113.63, 119.36, 121.23, 128.32, 128.37, 129.02, 129.46, 130.01, 133.49, 134.67,135.98, 136.17, 138.84, 149.35, 156.86, 159.65. MS (m/z): 326(M^+ + 1). Anal. Calc. for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91%. Found: C, 81.16; H, 5.94; N, 12.94%.

4-(2-Chlorophenylamino)-6-methyl-2-phenylquinazoline (3c). IR (KBr): 3430, 1533, 1356 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.58 (s, 3H, CH_3), 7.06-7.09 (m, 1H, ArH), 7.42-7.53 (m,

Table 2

Selected bond lengths (Å) and angles (°) for **3a**.

Bond lengths (Å)	
Cl(1)-C(21) 1.737(3)	N(2)-C(9) 1.364(3)
O(1)-C(2) 1.360(3)	N(3)-C(8) 1.374(3)
O(1)-C(1) 1.419(3)	N(3)-C(16) 1.404(2)
N(1)-C(9) 1.314(3)	C(5)-C(6) 1.409(3)
N(1)-C(5) 1.369(3)	C(6)-C(8) 1.431(3)
N(2)-C(8) 1.309(3)	C(9)-C(10) 1.486(3)
bond angles (°)	
C(2)-O(1)-C(1) 117.53(19)	N(2)-C(8)-N(3) 118.7(2)
C(9)-N(1)-C(5) 116.3(2)	N(2)-C(8)-C(6) 122.8(2)
C(8)-N(2)-C(9) 117.1(2)	N(3)-C(8)-C(6) 118.5(2)
C(8)-N(3)-C(16) 127.7(2)	N(1)-C(9)-N(2) 126.6(2)
C(7)-C(2)-O(1) 125.8(2)	N(1)-C(9)-C(10) 117.9(2)
C(7)-C(2)-C(3) 119.6(2)	N(2)-C(9)-C(10) 115.4(2)
O(1)-C(2)-C(3) 114.6(2)	C(21)-C(16)-N(3) 119.4(2)
N(1)-C(5)-C(4) 119.4(2)	C(17)-C(16)-N(3) 122.4(2)
N(1)-C(5)-C(6) 122.3(2)	C(20)-C(21)-Cl(1) 118.9(2)
C(4)-C(5)-C(6) 118.2(2)	C(16)-C(21)-Cl(1) 119.6(2)

Table 3

Crystal data and refinement details for **3a**.

Empirical formulas	$C_{21}H_{16}ClN_3O$
Formula weight	361.82
Temperature (K)	294 (2)
Wavelength (A)	0.71073
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	
a (Å)	12.536(3)
b (Å)	6.9533(17)
c (Å)	20.576(5)
Volume (Å^3)	1786.5(7)
Z	4
Crystal size (mm)	0.26 × 0.22 × 0.16
Calculate density (mg m^{-3})	1.345
Absorption coefficient (mm^{-1})	0.229
F(000)	752
Reflections collected/unique	9709/3662 [R(int) = 0.0781]
Completeness to theta = 26.41	99.6%
Data/restraints/parameters	3662/0/237
Limiting indices	$-12 <= h <= 15$, $-8 <= k <= 8$, $-21 <= l <= 25$
Goodness of fit on F^2	0.975
Final R indices [$I >$ 2sigma(I)]	$R1 = 0.0472$, $wR^2 = 0.0861$
R indices (all data)	$R1 = 0.1530$, $wR^2 = 0.1106$
Largest diff. peak and hole (e A^{-3})	0.192 and −0.262

4H, ArH), 7.62-7.64 (m, 2H, ArH), 7.89-7.90 (m, 1H, ArH), 8.09 (s, 1H, NH), 8.51-8.53 (m, 2H, ArH), 9.01 (dd, J_1 = 1.5 Hz, J_2 = 8.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 21.94, 114.04, 119.28, 122.03, 123.36, 123.68, 127.60, 128.32, 128.42, 129.11, 129.17, 130.16, 135.05, 135.49, 136.62, 138.61, 149.44, 156.35, 159.39. MS (m/z): 346(M^+ + 1). Anal. Calc. for $C_{21}H_{16}ClN_3$: C, 72.93; H, 4.66; N, 12.15%. Found: C, 72.87; H, 4.60; N, 12.20%.

4-(2-Chlorophenylamino)-2-phenylquinazoline (3d). IR (KBr): 3422, 1526, 1353 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.07-7.09 (m, 1H, ArH), 7.42-7.56 (m, 6H, ArH), 7.79-7.82 (m, 1H, ArH), 8.00 (d, J = 8.5 Hz, 1H, ArH), 7.90 (d, J = 8.5 Hz, 1H, ArH), 8.15 (s, 1H, NH), 8.53-8.55 (m, 2H, ArH), 9.00-9.02 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$): δ 114.22, 120.17, 122.11, 123.46, 123.84, 126.49, 127.63, 128.45, 128.48, 129.13, 129.47, 130.36, 133.05, 135.42, 138.54, 151.09, 156.85, 160.19. MS (m/z): 332(M^+ + 1). Anal. Calc. for $C_{20}H_{14}ClN_3$: C, 72.93; H, 4.25; N, 12.66%. Found: C, 72.85; H, 4.20; N, 12.58%.

6-Chloro-4-(2-chlorophenylamino)-2-phenylquinazoline (3e). IR (KBr): 3422, 1523, 1356 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.09-7.13 (m, 1H, ArH), 7.42-7.52 (m, 5H, ArH), 7.23 (dd, J_1 = 2.0 Hz, J_2 = 9.0 Hz, 1H, ArH), 7.84 (d, J = 4.0 Hz, 1H, ArH), 7.92 (d, J = 9.0 Hz, 1H, ArH), 7.97 (s, 1H, NH), 8.49-8.51 (m, 2H, ArH), 8.91 (dd, J_1 = 1.5 Hz, J_2 = 8.0 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$): δ 114.84, 119.71, 122.35, 123.75, 124.24, 127.61, 128.48, 128.49, 129.22, 130.59, 131.07, 131.89, 133.85, 135.08, 138.12, 149.67, 156.02, 160.40. MS (m/z): 366(M^+ + 1). Anal. Calc. for $C_{20}H_{13}Cl_2N_3$: C, 65.59; H, 3.58; N, 11.47%. Found: C, 65.65; H, 3.53; N, 11.53%.

6-Chloro-4-(4-methylphenylamino)-2-phenylquinazoline (3f). IR (KBr): 3431, 1525, 1353 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 7.25 (d, J = 3.5 Hz, 2H, ArH), 7.29 (s, 1H, NH), 7.46-7.49 (m, 3H, ArH), 7.67-7.71 (m, 3H, ArH), 7.79 (d, J = 2.5 Hz, 1H, ArH), 7.88 (d, J = 9.0 Hz, 1H, ArH), 8.49-8.51 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 20.95, 114.46, 119.84, 121.51, 128.38, 128.49, 129.50, 130.42, 130.78, 131.21, 133.43, 134.03, 135.64, 138.29, 149.53, 156.51, 160.61. MS (m/z): 346(M^+ + 1). Anal. Calc. for $C_{21}H_{16}ClN_3$: C, 72.93; H, 4.66; N, 12.15%. Found: C, 72.87; H, 4.59; N, 12.10%.

2-Phenyl-4-(phenylamino)quinazoline (3g). IR (KBr): 3273, 1520, 1367 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.12-7.20 (m, 1H, ArH), 7.44-7.52 (m, 7H, NH, ArH), 7.76-7.79(m, 1H, ArH), 7.84-7.90 (m, 3H, ArH), 7.98-7.99 (m, 1H, ArH), 8.54-8.56 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 113.82, 120.16, 121.26, 124.04, 126.07, 128.39, 128.50, 129.01, 129.37, 130.27, 132.86, 138.63, 138.66, 151.09, 157.29, 160.38. MS (m/z): 298(M^+ + 1). Anal. Calc. for $C_{20}H_{15}N_3$: C, 80.78; H, 5.08; N, 14.13%. Found: C, 80.74; H, 5.11; N, 14.19%.

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REFERENCES AND NOTES

[1] Abouzid, K.; Shouman, S. Bioorg Med Chem 2009, 17, 6796.

[2] Chilin, A.; Conconi, M. T.; Marzaro, G.; Guiotto, A.; Urbani, L.; Tonus, F.; Parnigotto, P. J Med Chem 2010, 53, 1862.

[3] Tsou, H. R.; Mamuya, N.; Johnson, B. D.; Reich, M. F.; Gruber, B. C.; Ye, F.; Nilakantan, R.; Shen, R.; Discafani, C.; DeBlanc, R.; Davis, R.; Koehn F. E., Greenberger, L. M.; Wang, Y. F.; Wissner, A. J Med Chem 2001, 44, 2719.

[4] Smaill, J. B.; Rewcastle, G. W.; Loo, J. A.; Greis, K. D.; Chan, O. H.; Reyner, E. L.; Lipka, E.; Showalter, H. D.; Vincent, P. W.; Elliott, W. L.; Denny, W. A. J Med Chem 2000, 43, 1380.

[5] Amin, K. M.; Kamel, M. M.; Anwar, M. M.; Khedr, M.; Syam, Y. M. Eur J Med Chem 2010, 45, 2117.

[6] Xu G. F.; Song, B. A.; Bhadury, P. S.; Yang, S.; Zhang, P. Q.; Jin, L. H.; Xue, W.; Hu, D. Y.; Lu, P. Bioorg Med Chem 2007, 15, 3768.

[7] Rohini, R.; Reddy, P. M.; Shanker, K.; Hu, A.; Ravinder, V. Eur J Med Chem 2010, 45, 1200.

[8] Alagarsamy, V.; Pathak, U. S. Bioorg Med Chem 2007, 15, 3457.

[9] Ismail, M. A. H.; Aboul-Enein, M. N. Y.; Abouzid, K. A. M.; Serya, R. A. T. Bioorg Med Chem 2006, 14, 898.

[10] Shreder, K. R.; Wong, M. S.; Nomanbhoy, T.; Leventhal, P. S.; Fuller, S. R. Org Lett 2004, 6, 3715.

[11] (a) Wang, X.B; Song, A. M.; Dixon, S.; Kurth, M. J.; Lam, K. S.; Tetrahedron Lett 2005, 46, 427; (b) Okuzumi, T.; Nakanishi, E.; Tsuji, T.; Makino, S. Tetrahedron 2003, 59, 5603.

[12] (a) Chilin, A.; Marzaro, G.; Zanatta, S.; Guiotto, A. Tetrahedron Lett 2007, 48, 3229. (b) Li, G.; Kakarla, R.; Gerritz, S. W.; Pendri, A.; Ma, B. Q. Tetrahedron Lett 2009, 50, 6048.

[13] Maitraie, D.; Yakaiah, T.; Srinivas, K.; Reddy, G. V.; Ravikanth, S.; Narsaiah, B.; Rao, P. S.; Ravikumar, K.; Sridhar, B. J Fluorine Chem 2006, 127, 351.

[14] Marzaro, G.; Guiotto, A.; Pastorini, G.; Chilin, A. Tetrahedron 2010, 66, 962.

[15] (a) Wang, M. M.; Dou, G. L.; Shi, D. Q. J Comb Chem 2010, 12, 582. (b) Blank, J.; Kandt, M.; Pfeiffer, W. D. Hetzheim, A.; Langer, P. Eur J Org Chem 2003, 2003, 182.

[16] Jayanthi, G.; Muthusamy, S.; Ramakrishnan, V. T. J Photoch Photobio A: Chem 1998, 116, 103.

[17] Senthilvelan, A.; Ramakrishnan, V. T. Tetrahedron Lett 2002, 43, 5119.

[18] Senthilvelan, A.; Thirumalai, D.; Ramakrishnan, V. T. Tetrahedron 2004, 60, 851.

[19] Van den nieuwendijk, A. M. C. H.; Pietra, D.; Heitman, L.; Göblyös, A.; IJzerman, A. P. J Med Chem 2004, 47, 663.