Synthesis of Potentially Photoactivatable Coumarin Derivatives *via* a 1,3-Dipolar Cycloaddition

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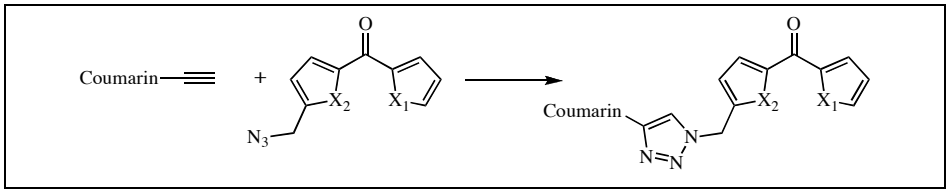

A copper (I)-catalyzed 1,3-dipolar cycloaddition reaction was used to prepare a series of mono and disubstituted 1,2,3-triazolyl-coumarins using a 1,3-cycloaddition ("Click Chemistry"). Starting coumarins were synthesized using classical or modified Pechmann's reaction. The propargyl group was introduced as either propargylether or as a propargylamide. Azides were prepared in a three steps procedure. Cycloaddition products, containing a coumarin and a photoactivatable moiety, were obtained in good yields.

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INTRODUCTION

1,3-Dipolar cycloaddition reactions are very useful in synthetic organic chemistry. One of them is the Huisgen reaction [1], which was recently improved and named "Click Chemistry" by Sharpless *et al*. [2] This consists in a cycloaddition reaction between an azide and a terminal alkyne. The regioselectivity of this reaction, controlled by the introduction of catalytic quantities of copper (I), allows the exclusive formation of a 1,4-disubstituted 1,2,3-triazole [3]. Moreover, utilization of the catalyst increases the reaction rate and allows the reaction to proceed at room temperature. The range of application of this reaction has been constantly increasing. Its tolerance to a large variety of functional groups, ease to carry out and good yields, make this method a very useful synthetic tool. This reaction has been applied in order to selectively modify biomolecules and living cells [4], synthesize pseudopeptide conjugates [5] and recently, coumarin-nucleoside conjugates [6].

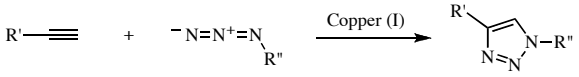
On the other hand, coumarins have a wide spectrum of biological activities and uses [7-14]. Moreover, coumarins constitute an important class of organic fluorescent dyes. These fluorescent properties have been used to study proteins and nucleic acids [15,16].

Recent articles exposed the use *via* click chemistry of some of coumarin derivatives [17]. As a continuation of our research about photolabeling of proteins [18], we choose to combine, *via* a triazole formed by click chemistry, benzophenone and thiophene analogues to coumarins in order to prepare new photoactivatable agents for proteins labeling.

Benzophenones are often used for photoaffinity labeling (PAL) [19,20]. The photolabeling principle is to form, by UV-irradiation, a covalent bond between the tag which contains the photoactivatable group and enzymes or proteins. This technique allows the access to a large amount of structural information and it is a good tool to identify molecular interaction sites. Detection of the labeled proteins through fluorescence can be achieved using the photophysical properties of coumarins. Introducing propargyl chains as coumarin side chains and azides on the benzophenones gave the starting material for the click chemistry.

In this paper, the 1,3-dipolar cycloaddition between terminal alkynes (coumarin derivatives, compound **a**) and azides (benzophenone or analogues, compound **b**) was performed using $CuSO_4.5H_2O$ and sodium ascorbate as catalytic system in DMF (Scheme I).

Scheme I



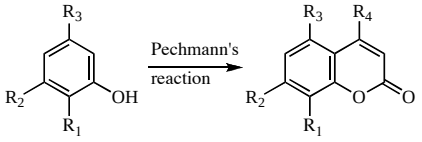
a **b**

RESULTS AND DISCUSSION

We have developed in our laboratory an environmental friendly procedure to synthesize some hydroxy substituted coumarins, (see compounds **1-3**) [21], in good yields. Only, coumarin-4-acetic acid **4** was obtained by a classical Pechmann reaction (Table 1).

Table 1

Prepared hydroxy coumarins and coumarinyl-4-acetic acid.



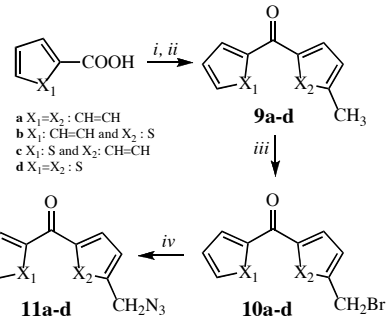
1-4

Compd	R_1	R_2	R_3	R_4	Yields (%)
1	H	OH	H	CH_3	91[i or ii]
2	OH	OH	H	CH_3	52[i]/64[ii]
3	H	OH	OH	CH_3	92[i]/48[ii]
4	CH=CH-CH=CH		H	CH_2COOH	36[iii]

Reaction conditions : *i*. SZr, b-ketoester, 80 °C, 24h or 60-65 °C, 24h; *ii*. $ZrOCl_2.8H_2O$, beta-ketoester, 80 °C, 24h or 60-65 °C, 24h; *iii*. 1,3-acetone dicarboxylic acid, sulfuric acid

The terminal alkyne group was introduced as either a propargylether for **1-3** or a propargylamide for **4**. Propargylethers **5-7** were prepared by reacting coumarins **1-3** with propargylbromide in dry acetone in presence of dry potassium carbonate. Amidification of compound **4** to yield propargyl amide **8** was done by activating the acid (NHS, DCC) and reacting the ester with propargylamine. The "one pot" reaction gave amide **8** in 57% yield (Table 2).

Scheme II

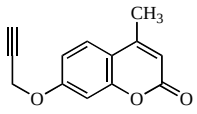
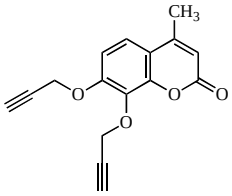
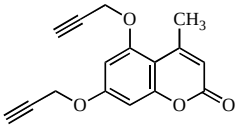
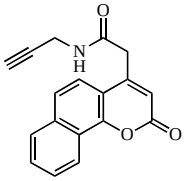


Reaction conditions: *i*. $SOCl_2$; *ii*. toluene or 2-methylthiophene, $AlCl_3$, DCM; *iii*. NBS, AIBN, DCM; *iv*. NaN_3, DMF, 50 °C.

reaction (Scheme II). Acyl chlorides were prepared from benzoic acid or 2-thiophenecarboxylic acid and thionyl chloride, and reacted with toluene or 2-methylthiophene in presence of aluminium chloride. The residual methyl chain in those di-(het) aryl-ketones was then transformed by radical substitution using NBS to obtain bromo-derivatives **10a-d** as mixtures with unreacted **9**. The mixture was reacted with sodium azide without further purification and expected azides **11a-d** were obtained in good yields (56-85 %) after final column chromatography purification.

Table 2

Prepared terminal alkyne coumarins

Compd	Starting coumarins	Product	Yields (%)	Compd	Starting coumarins	Product	Yields (%)
5	1		90[i]	7	3		80[i]
6	2		91[i]	8	4		57[ii]

Reaction conditions: i. K_2CO_3, propargylbromide, dry acetone; ii. NHS, DCC, propargylamine, DMF".

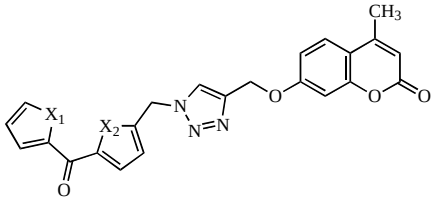
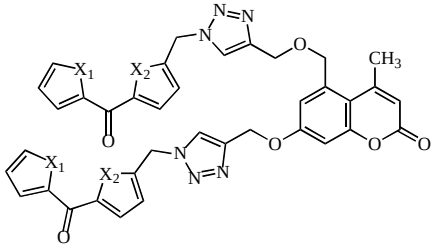
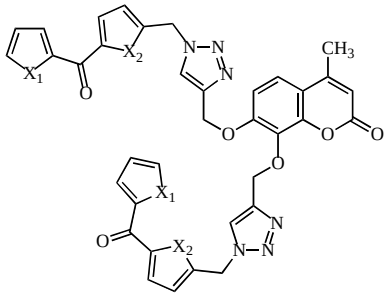
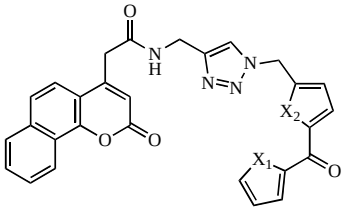
On the other hand, the azido function was introduced on benzophenone analogues. For this purpose a three-step procedure was developed to synthesize 4-azidomethyl-benzophenone and thiophene analogues (Scheme II).

The synthesis of 4-methylbenzophenone **9a** is well documented in the literature [22] contrary to thiophene analogues **9b-d**. Only several examples of them have been reported [23], being **9d** the less described **[**24]. Compounds **9a-d** were prepared by a Friedel-Crafts

Classical conditions were used ($CuSO_4.5H_2O$ and sodium ascorbate) for the Cu (I)-catalyzed Huisgen 1,3-dipolar cycloaddition. Reactions were performed in DMF in order to increase the starting material solubility and to simplify the work up. After 36 h at room temperature reactions were quenched with water. The formed precipitate was collected by filtration, washed with water and dried at room temperature until constant weight. Recrystallization from diethyl ether gave compounds **12a-**

Table 3

Coumarin derivatives obtained by a copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition.

Alkynes	Azides	Click Chemistry Product	Compd	Yields (%)
5	**11a**		**12a**	98
	11b		**12b**	97
	11c		**12c**	56
	11d		**12d**	94
6	**11a**		**13a**	74
	11b		**13b**	74
	11c		**13c**	89
	11d		**13d**	86
7	**11a**		**14a**	92
	11b		**14b**	53
	11c		**14c**	89
	11d		**14d**	95
8	**11a**		**15a**	92
	11b		**15b**	96
	11c		**15c**	97
	11d		**15d**	65

d, **13a-d**, **14a-d** and **15a-d** in good yields. Results are listed in Table 3.

CONCLUSION

Some alkyne substituted coumarins and thiophene benzophenone analogues have been synthesized and coupled using the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition in order to obtain new potentially photoactivatable compounds. The latter have been described for the first time and fully characterized. The ability of some of them to perform photoaffinity labeling of proteins is actually under investigation and results will be published when due.

EXPERIMENTAL

Reagents and solvents used in this work were obtained from Acros Organics. Melting points were measured on a Stuart Scientific SMP3 apparatus and are uncorrected. MALDI-FTICRMS (Matrix Assisted Laser Desorption/Ionization coupled to Fourier Transform Ion Cyclotron Resonance Mass Spectrometry) measurements were carried out on an IonSpec Explorer Fourier Transform Mass Spectrometer 9.4 T equipped with a ProMALDI module (IonSpec, Lake Forest, USA) provided with an Orion air cooled Nd:YAG System (355 nm, New wave research, Fremont, USA). The matrix used was a saturated 2,5-dihydroxybenzoic acid (2,5-DHB) solution in 50% methanol, 0.1% trifluoro acetic acid (TFA). All the depositions were made using the dried-droplet method. All the spectrum were internally calibrated using a methotrexate solution (1.10^{-6}

M) and the peak used to create a calibration list was methotrexate's $[M+H]^+$ pseudomolecular ion at m/z = 455.17859 Da. Gc/ms spectra measurements were performed on a Hewlett-Packard 5971A electron impact (70eV) mass spectrometer, equipped with a Hewlett Packard 5890 series II gas chromatograph. ^1H and ^{13}C nmr spectra were recorded on a Bruker-AC 250-M Hz spectrometer with $CDCl_3$ or DMSO-d_6 as both solvent and internal reference. The chemical shifts (δ) are expressed in ppm and coupling constants (J) in Hz. Compounds **1-3** were prepared as described in the literature [21].

(2-Oxo-*2H*-benzo[*h*]chromen-4-yl)-acetic acid (4). 1-Naphthol (4.9 g, 34.22 mmol) and 1,3-acetone dicarboxylic acid (5 g, 34.22 mmol) were added to sulfuric acid (25 mL). The mixture was stirred overnight at room temperature and poured onto water. The obtained precipitate was washed with water and dried *in vacuo* until constant weight yielding 3.13 g, 36 %, as a pink solid, mp 207-208 °C (mp_{lit} 212-213 °C [25]). ^1H nmr (DMSO-d_6): δ 8.38-8.34 (m, 1H), 8.04-8.00 (m, 1H), 7.84 (d, 1H, J= 7.5 Hz), 7.74-7.69 (m, 2H), 6.61 (s, 1H), 4.00 (s, 2H, C*H*$_2$). ^{13}C nmr (DMSO-d_6): δ 170.6, 159.5, 150.8, 149.9, 134.2, 128.7, 127.9, 127.4, 123.9, 122.2, 121.5, 121.3, 115.8, 114.6, 37.5.

Methyl-7-(2-propynyloxy)-*2H*-chromen-2-one (5). To a solution of 7-hydroxy-4-methylcoumarin (4-methylumbelliferone) (2.64 g, 15 mmol) in 40 mL of dry acetone was added anhydrous potassium carbonate (2.07 g, 15 mmol) and propargyl bromide (1.67 mL, 15 mmol). The mixture was stirred at 50 °C for 18 h. After that time, the solvent was removed under reduced pressure. The residue was treated with 20 mL of water and extracted with ethyl acetate. Organic phases were combined and washed with a 0.1 *N* sodium hydroxide solution and twice with water. The organic layer was dried, filtered and solvent was removed *in vacuo*. Crystallization from diethyl ether gave (2.89 g), 90 %, beige solid, mp 135-136 °C (mp_{lit} 134 °C 26). ^1H nmr ($CDCl_3$): δ 7.55-7.51 (m, 1H), 6.95-6.91 (m, 2H), 6.17 (s, 1H), 4.74 (d, 2H, J=2.3 Hz), 2.57 (t, 1H, J=2.3 Hz), 2.41 (d, 3H, C*H*$_3$, J=1.2 Hz). nmr ($CDCl_3$): δ 161.1, 160.3, 155.0, 152.4, 125.6, 114.2, 112.7, 112.4, 102.1, 77.4, 56.2, 18.7. hrms-maldi : *m/z* $[M+H]^+$ calcd for $C_{13}H_{10}O_3$: 215.07027, found : 215.07023.

General procedure for the preparation of compounds 6 and 7. Compounds **6** and **7** were obtained from 5,7-dihydroxy-4-methyl-*2H*-chromen-2-one and 7,8-dihydroxy-4-methyl-*2H*-chromen-2-one respectively, using the same procedure as for **5**. In this case twice of molar quantities of anhydrous potassium carbonate and propargyl bromide was employed.

4-Methyl-5,7-bis (2-propynyloxy)-*2H*-chromen-2-one (6). (3.64 g), 91 %, beige solid, mp 186-188 °C. ^1H nmr ($CDCl_3$): δ 6.59 (d, 1H, J=2.5 Hz), 6.47 (d, 1H, J=2.5 Hz), 6.00 (d, 1H, J=1.2 Hz), 4.75 (d, 2H, J=2.5 Hz), 4.74 (d, 2H, J=2.5 Hz), 2.60-2.49 (m, 5H). ^{13}C nmr ($CDCl_3$): δ 160.7, 160.2, 156.9, 156.7, 154.0, 112.3, 105.8, 97.3, 95.4, 77.2, 56.5, 56.2, 24.3. hrms-maldi: *m/z* $[M+H]^+$ calcd for $C_{16}H_{12}O_4$: 269.08084, found : 269.08083.

4-Methyl-7,8-bis(2-propynyloxy)-*2H*-chromen-2-one (7). (3.22 g), 80 %, yellow solid, mp 135-137 °C. ^1H nmr ($CDCl_3$): δ 7.35 (d, 1H, J=9.0 Hz), 7.05 (d, 1H, J=9.0 Hz), 6.18 (d, 1H, J=1.2 Hz), 4.90 (d, 2H, J=2.4 Hz), 4.87 (d, 2H, J=2.4 Hz), 2.55 (t, 1H, J=2.4 Hz), 2.44 (t, 1H, J=2.4 Hz), 2.41 (d, 3H, C*H*$_3$, J=1.2 Hz). ^{13}C nmr ($CDCl_3$): δ 160.2, 153.5, 152.4, 148.2, 134.2, 120.0, 115.5, 112.9, 110.2, 78.5, 77.7, 77.2, 75.9, 60.6, 57.0, 18.8. hrms-maldi: *m/z* $[M+H]^+$ calcd for $C_{16}H_{12}O_4$: 269.08084, found : 269.08087.

2-(2-Oxo-*2H*-benzo[*h*]chromen-4-yl)-N-(2-propyn-yl)-acetamide (8). To a solution of (2-oxo-*2H*-benzo[*h*]-chromen-4-yl)acetic acid (1 g, 3.93 mmol) in dry dimethylformamide (5 mL) were added *N*-hydroxysuccinimide (0.476 g, 4.13 mmol) and *N,N'*-dicyclohexylcarbodiimide (1.7 g, 8.28 mmol) in dimethylformamide (5 mL). The mixture was stirred at room temperature for 24 h, then propargylamine (0.276 mL, 4.02 mmol) was added and left to stir overnight at the same temperature. The formed precipitate was filtered. The obtained filtrate was poured into water, filtrated, washed with water and dried at room temperature until constant weight. Pure product was obtained by cristallisation from diethyl ether. (0.65 g), 57 %, dark beige solid, mp 245-246 °C. ^1H nmr (DMSO-d_6): δ 8.71 (t, 1H, N*H*, J=5.3 Hz), 8.38-8.34 (m, 1H), 8.05-8.00 (m, 1H), 7.84 (d, 1H, J=8.7 Hz), 7.74-7.69 (m, 3H), 6.55 (s, 1H), 3.93-3.88 (m, 4H), 3.17 (t, 1H, J=2.5 Hz). ^{13}C nmr (DMSO-d_6): δ 167.5, 159.5, 151.4, 149.9, 134.2, 128.7, 127.9, 127.4, 123.9: 122.2, 121.5, 121.2, 115.6, 114.6, 80.7, 73.2, 39.7, 28.2. hrms-maldi: *m/z* $[M+H]^+$ calcd for $C_{18}H_{13}NO_3$: 292.09682, found : 292.09687.

General procedure for the preparation of compounds 9 (a-d). To benzoic acid (1.22 g, 10 mmol) or 2-thiophenecarboxylic acid (1.28 g, 10 mmol) was added thionyl chloride (10 mL). The mixture was refluxed for 4 h. Thionyl chloride excess was evaporated *in vacuo*. To the obtained acid chloride was added toluene (2.13 mL, 20 mmol) or 2-methylthiophene (1.94 mL, 20 mmol) in dichloromethane (20 mL), and aluminium chloride (2 g, 15 mmol) by portions. The mixture was stirred for 4 h at room temperature and hydrolyzed with concentrated hydrochloric acid (4 mL) in iced-water (50 mL). The product was extracted with ethyl acetate. The organic layer was washed twice with water, dried and solvent was removed until dryness. Pure products were obtained after purification by column chromatography using dichloromethane as eluent.

(4-Methylphenyl)(phenyl)methanone (9a). (1.41 g), 72 %, yellow solid, mp_{lit} 56.5-57 °C [22]. ^1H nmr ($CDCl_3$): 7.83-7.77 (m, 2H), 7.75 (d, 2H, J=7.9Hz), 7.62-7.56 (m, 1H), 7.51-7.44 (m, 2H), 7.29 (d, 2H, J=7.9 Hz), 2.45 (s, 3H, C*H*$_3$). ^{13}C nmr ($CDCl_3$): 196.5, 143.2, 138.0, 134.9, 132.1, 130.3, 129.9, 129.0, 128.2, 21.6. gc/ms: *m/z* (%): 196 (71, M^+), 181 (21), 119 (100), 105 (27), 91 (39).

(5-Methyl-2-thienyl)(phenyl)methanone (9b). (1.80 g), 89 %, brown oil. ^1H nmr ($CDCl_3$): δ 7.83 (d, 2H, J=7.5 Hz), 7.60-7.53 (m, 1H), 7.51-7.45 (m, 3H), 6.83 (d, 1H, J=3.6 Hz), 2.58 (s, 3H, C*H*$_3$). ^{13}C nmr ($CDCl_3$): δ 188.1, 150.4, 141.6, 138.3, 135.7, 132.0, 129.0, 128.3, 126.7, 16.1. gc/ms: m/z (%): 202 (98, M^+), 187 (11), 125 (100), 105 (16), 97 (10).

(4-Methylphenyl)(2-thienyl)methanone (9c). (0.97 g), 48 %, brown-pink solid, mp 72-75 °C. ^1H nmr ($CDCl_3$): δ 7.79 (d, 2H, J=8.1 Hz), 7.70 (d, 1H, J=4.7 Hz), 7.65 (d, 1H, J=3.6 Hz), 7.30 (d, 2H, J=8.1 Hz), 7.16 (dd, 1H, J=3.6, 4.7 Hz), 2.45 (s, 3H, C*H*$_3$). ^{13}C nmr ($CDCl_3$): δ 187.7, 143.9, 143.0, 135.4, 134.4, 133.8, 129.4, 129.1, 127.8, 21.6. gc/ms: m/z (%): 202 (100, M^+), 187 (43), 119 (87), 111 (67), 91 (43).

(5-Methyl-2-thienyl)(2-thienyl)methanone (9d). (1.00 g), 48 %, brown solid, mp 50-52 °C. ^1H nmr ($CDCl_3$): δ 7.84 (d, 1H, J=3.6 Hz), 7.72 (d, 1H, J=3.6 Hz), 7.66 (d, 1H, J=4.9 Hz), 7.17 (dd, 1H, J=3.6, 4.9 Hz), 6.85 (d, 1H, J=3.6 Hz), 2.57 (s, 3H, C*H*$_3$). ^{13}C nmr ($CDCl_3$): δ 178.4, 149.7, 143.0, 140.7, 133.9, 133.0, 132.7, 127.8, 126.7, 15.9. gc/ms: m/z (%): 208 (M^+,100), 125 (69), 11 (31), 97 (8).

General procedure for the preparation of compounds 10 (a-d). To a solution of compounds **9a-d** (5 mmol) in dichloromethane (15 mL) was added a catalytic amount of α,α'-azodiisobutyronitrile. The mixture was refluxed for 30 min with a 500 W-halogen lamp and *N*-bromosuccinimide (1.07 g, 6 mmol) was added in three portions and left to stir at reflux for 2 h. The reaction was quenched with water. The organic layer was washed with water, dried and evaporated until dryness. The crude product was directly used in the next step without further purification.

General procedure for the preparation of compounds 11 (a-d). The above obtained mixture (compounds **9** and **10**) was dissolved in dimethylformamide (20 mL) and sodium azide (0.326 g, 5 mmol) was added. The resultant mixture was heated at 50 °C for 3 h, then water (50 mL) was added at room temperature and left to stir overnight. The mixture was dissolved with diethyl ether (25 mL) and washed with water, dried and concentrated until dryness. Pure product was obtained after purification by column chromatography using dichloromethane as eluent.

[4-(Azidomethyl)phenyl](phenyl)methanone (11a). (098 g), 83 % (2steps), yellow oil. ^{1}H nmr ($CDCl_3$): δ 7.85-7.79 (m, 4H), 7.64-7.58 (m, 1H), 7.53-7.43 (m, 4H), 4.46 (s, 2H, CH_2N$_3$). ^{13}C nmr ($CDCl_3$): δ 196.1, 140.0, 137.4, 132.6, 130.6, 130.0, 128.4, 127.9, 54.3.

[5-(Azidomethyl)-2-thienyl](phenyl)methanone (11b). (0.68 g), 56 % (2 steps), orange solid, mp 33 °C. ^{1}H nmr ($CDCl_3$): δ 7.85 (d, 2H, J=7.3 Hz), 7.64-7.48 (m, 4H), 7.09 (d, 1H, J=3.7 Hz), 4.56 (s, 2H, CH_2N$_3$). ^{13}C nmr ($CDCl_3$): δ 187.9, 146.6, 143.9, 137.7, 134.8, 132.4, 129.1, 128.6, 127.4, 49.3.

[4-(Azidomethyl)phenyl](2-thienyl)methanone (11c). (1.03 g), 85 % (2steps), yellow solid, mp 42 °C. ^{1}H nmr ($CDCl_3$): δ 7.88 (d, 2H, J=7.9 Hz), 7.73 (d, 1H, J=4.9 Hz), 7.64 (d, 1H, J=3.7 Hz), 7.45 (d, 2H, J=7.9 Hz), 7.17 (dd, 1H, J=3.7, 4.9 Hz), 4.45 (s, 2H, CH_2N$_3$). ^{13}C nmr ($CDCl_3$): δ 187.5, 143.4, 139.8, 138.0, 134.8, 134.4, 129.7, 128.0, 54.3.

[5-(Azidomethyl)-2-thienyl](2-thienyl)methanone (11d). (0.97 g), 78 % (2steps), yellow oil. ^{1}H nmr ($CDCl_3$): δ 7.90 (d, 1H, J=3.6 Hz), 7.80 (d, 1H, J=3.6 Hz), 7.72 (d, 1H, J=4.9 Hz), 7.20 (dd, 1H, J=4.9, 3.8 Hz), 7.12 (d, 1H, J=3.8 Hz), 4.57 (s, 2H, CH_2N$_3$). ^{13}C nmr ($CDCl_3$): δ 178.4, 145.9, 143.2, 142.5, 133.7, 133.2, 128 .4, 128.0, 127.4, 49.3.

General procedure for the preparation of compounds 12 (a-d). A suspention of $CuSO_4$•5H_2O (0.025 g, 0.1 mmol) and sodium ascorbate (0.04 g, 0.2 mmol) in dimethylformamide (0.5 mL) was stirred at room temperature for 15 min, then compound **5** (0.22 g, 1 mmol) in dimethylformamide (0.5 mL) was added. After the mixture changed color, a suspension of compounds **11a-d** (1.01 mmol) in dimethylformamide (0.5 mL) was added dropwise. The mixture was stirred for 36 h at room temperature in the absence of light. The reaction was stopped by the addition of water (10 mL). The obtained precipitate was collected by filtration, washed with water and dried at room temperature until constant weight. Crystallization from diethyl ether yields the pure product.

7-{[1-(4-Benzoylbenzyl)-*1H*-1,2,3-triazol-4-yl]methoxy}-4-methyl-*2H*-chromen-2-one (12a). (0.44 g), 98 %, pale yellow solid, mp 139-140 °C. ^{1}H nmr ($CDCl_3$): δ 7.80 (t, 4H, J=8.0 Hz), 7.64-7.59 (m, 2H), 7.52-7.46 (m, 3H), 7.38 (d, 2H, J=8.0 Hz), 6.96-6.92 (m, 2H), 6.15 (s, 1H), 5.65 (s, 2H, NCH_2), 5.27 (s, 2H, OCH_2), 2.40 (s, 3H, CH_3). ^{13}C nmr ($CDCl_3$): δ 195.8, 161.1, 161.0, 155.1, 152.4, 138.5, 138.1, 137.1, 132.8, 130.8, 130.0, 128.4, 127.8, 125.7, 123.0, 114.1, 112.4, 112.3, 102.1, 77.2, 62.3, 53.9, 18.7. hrms-maldi: m/z [M+H]$^+$ calcd for $C_{27}H_{21}N_3O_4$: 452.16048, found : 452.16049.

7-({1-[(5-Benzoyl-2-thienyl)methyl]-*1H*-1,2,3-triazol-4-yl}-methoxy)-4-methyl-*2H*-chromen-2-one (12b). (0.44 g), 97 %, pale yellow solid, mp 108-111 °C. ^{1}H nmr ($CDCl_3$): δ 7.78 (d, 2H, J=7.2 Hz), 7.73 (s, 1H), 7.59 (m, 1H), 7.54-7.47 (m, 4H), 7.14 (d, 1H, J=4.0 Hz), 6.97-6.92 (m, 2H), 6.15 (s. 1H), 5.78 (s, 2H, NCH_2), 5.27 (s, 2H, OCH_2), 2.40 (s, 3H, CH_3). ^{13}C nmr ($CDCl_3$): δ 187.7, 161.2, 161.0, 155.1, 152.5, 144.7, 144.5, 137.3, 134.8, 132.7, 129.1, 128.6, 125.7, 122.9, 114.1, 112.4, 112.3, 102.1, 77.2, 62.2, 48.8, 18.6. hrms-maldi: m/z [M+H]$^+$ calcd for $C_{25}H_{19}N_3O_4S$: 458.11690, found : 458.11697.

4-Methyl-7-({1-[4-(2-thienylcarbonyl)benzyl]-*1H*-1,2,3-triazol-4-yl}methoxy)-*2H*-chromen-2-one (12c). (0.26 g), 56 %, light yellow solid, mp 144-146 °C. ^{1}H nmr ($CDCl_3$): δ 7.87 (d, 2H, J=8.0 Hz), 7.75 (dd, 1H, J=4.9, 1.1 Hz), 7.65 (s, 1H), 7.62 (dd, 1H, J=3.8, 1.1 Hz), 7.51 (d, 1H, J=8.7 Hz), 7.40 (d, 2H, J=7.8 Hz), 7.17 (dd, 1H, J=4.5, 3.8 Hz), 6.97-6.93 (m, 2H), 6.16 (s, 1H), 5.65 (s, 2H, NCH_2), 5.27 (s, 2H, OCH_2), 2.40 (s, 3H, CH_3). ^{13}C nmr ($CDCl_3$): δ 187.3, 164.8, 161.1, 161.0, 155.1, 152.4, 138.6, 138.4, 135.0, 134.7, 130.0, 128.1, 128.0, 125.7, 114.1, 112.4, 112.3, 102.1, 77.2, 62.2, 53.8, 18.7. hrms-maldi: m/z [M+H]$^+$ calcd for $C_{25}H_{19}N_3O_4S$: 458.11690, found : 458.11679.

4-Methyl-7-[(1-{[5-(2-thienylcarbonyl)-2-thienyl]methyl}-*1H*-1,2,3-triazol-4-yl) methoxy]-*2H*-chromen-2-one (12d). (0.44 g), 94 %, yellow solid, mp 173-175 °C. ^{1}H nmr ($CDCl_3$): δ 7.86 (dd, 1H, J=3.8, 1.1 Hz), 7.77 (d, 1H, J=3.8 Hz), 7.73-7.70 (m, 2H), 7.51 (d, 1H, J=8.7 Hz), 7.21-7.15 (m, 2H), 6.96-6.91 (m, 2H), 6.14 (s, 1H), 5.78 (s, 2H, NCH_2), 5.26 (s, 2H, OCH_2), 2.39 (s, 3H, CH_3). ^{13}C nmr ($CDCl_3$): δ 178.2, 161.1, 161.0, 155.1, 152.4, 144.1, 143.7, 142.2, 134.0, 133.4, 133.0, 128.6, 128.1, 125.7, 114.1, 112.4, 112.3, 102.1, 77.2, 62.2, 48.7, 29.7. hrms-maldi: m/z [M+H]$^+$ calcd for $C_{23}H_{17}N_3O_4S_2$: 464.07332, found : 464.07331.

General procedure for the preparation of compounds 13 (a-d) and 14 (a-d). Compounds **13a-d** and **14a-d** were obtained from 4-Methyl-5,7-bis(2-propynyloxy)-*2H*-chromen-2-one **6** and 4-Methyl-7,8-bis(2-propynyloxy)-*2H*-chromen-2-one **7** respectively, using the same procedure as for **12a-d** and twice of molar quantities of compounds **11a-d**.

5,7-Bis{[1-(4-benzoylbenzyl)-*1H*-1,2,3-triazol-4-yl]methoxy}-4-methyl-*2H*-chromen-2-one (13a). (0.55 g), 74 %, beige solid, mp 99-100 °C. ^{1}H nmr ($CDCl_3$): δ 7.82-7.75 (m, 8H), 7.66 (d, 2H, J=3.7 Hz), 7.64-7.58 (m, 2H), 7.48 (dd, 4H, J=7.3, 1.0 Hz), 7.37 (t, J=7.3 Hz, 4H), 6.54 (dd, 2H, J=7.3, 2.2 Hz), 5.91 (d, 1H, J=1.2 Hz), 5.65 (d, 4H, NCH_2, J=3.7 Hz), 5.21 (s, 4H, OCH_2), 2.42 (s, 3H, CH_3). ^{13}C nmr ($CDCl_3$): δ 195.8, 161.2, 161.0, 157.5, 156.7, 154.4, 154.0, 143.5, 143.3, 138.6, 138.1, 137.0, 132.8, 130.8, 130.0, 128.4, 127.9, 127.7, 123.3, 111.9, 105.3, 96.8, 95.2, 77.2, 62.5, 62.1, 53.8, 24.4. hrms-maldi: m/z [M+H]$^+$ calcd for $C_{44}H_{34}N_6O_6$: 743.26126, found : 743.26116.

5,7-Bis({1-[(5-benzoyl-2-thienyl)methyl]-*1H*-1,2,3-triazol-4-yl}methoxy)-4-methyl-*2H*-chromen-2-one (13b). (0.56 g), 74 %, beige solid, mp 156-158 °C. ^{1}H nmr ($CDCl_3$): δ 7.84-7.78 (m, 6H), 7.64-7.58 (m, 2H), 7.53-7.47 (m, 6H), 7.14 (t, 2H, J=3.7 Hz), 6.54 (dd, 2H, J=9.0, 2.2 Hz), 5.92 (s, 1H), 5.80 (s, 2H, NCH_2), 5.79 (s, 2H, NCH_2), 5.22 (s, 4H, OCH_2), 2.44 (s, 3H, CH_3). ^{13}C nmr ($CDCl_3$): δ 187.7, 161.0, 160.7, 157.5, 156.8, 154.0, 144.8, 144.5, 144.4, 143.4, 137.3, 134.7, 132.7, 129.1, 128.6, 128.5, 123.0, 112.0, 105.5, 96.9, 95.4, 77.2, 62.4, 62.0,

48.9, 48.8, 23.4. hrms-maldi: m/z $[M+H]^+$ calcd for $C_{40}H_{30}N_6O_6S_2$: 755.17410, found : 755.17432.

4-Methyl-5,7-bis({1-[4-(2-thienylcarbonyl)benzyl]-*1H*-1,2,3-triazol-4-yl}methoxy)-*2H*- chromen-2-one (13c). (0.67 g), 89 %, light yellow solid, mp 147-150 °C. ^{1}H nmr ($CDCl_3$): δ 7.86 (d, 4H, J=8.0 Hz), 7.76-7.74 (m, 2H), 7.68 (d, 2H, J=5.0 Hz), 7.62-7.60 (m, 2H), 7.38 (t, 4H, J=8.0 Hz), 7.18-7.15 (m, 2H), 6.53 (dd, 2H, J=7.8, 2.3 Hz), 5.91 (d, 1H, J=1.2 Hz), 5.66 (s, 2H, NCH_2), 5.65 (s, 2H, NCH_2), 5.21 (s, 4H, OCH_2), 2.42 (s, 3H, CH_3). ^{13}C nmr ($CDCl_3$): δ 187.3, 161.0, 160.7, 157.6, 156.8, 154.0, 143.3, 143.2, 142.6, 138.6, 138.5, 138.4, 135.0, 134.8, 134.7, 130.0, 128.2, 128.0, 127.9, 123.2, 113.7, 112.0, 105.4, 96.9, 95.3, 77.2, 62.5, 62.1, 53.8, 24.4. hrms-maldi: m/z $[M+H]^+$ calcd for $C_{40}H_{30}N_6O_6S_2$: 755.17410, found : 755.17424.

4-Methyl-5,7-bis[(1-{[5-(2-thienylcarbonyl)-2-thienyl]methyl}-*1H*-1,2,3-triazol-4-yl)methoxy]-*2H*-chromen-2-one (13d). (0.66 g), 86 %, dark beige solid, mp 192-195 °C. ^{1}H nmr (DMSO-d_6): δ 8.42 (d, 2H, J=1.2 Hz), 8.09 (d, 2H, J=4.7 Hz), 8.02 (d, 2H, J=3.7 Hz), 7.94 (d, 2H, J=3.7 Hz), 7.31-7.27 (m, 4H), 6.79 (s, 1H), 6.77 (s, 1H), 5.98-5.96 (m, 5H), 5.27 (s, 4H), 2.36 (s, 3H, CH_3). ^{13}C nmr (DMSO-d_6): δ 177.7, 161.1, 159.5, 157.4, 156.2, 153.9, 146.6, 146.4, 142.4, 142.3, 141.6, 135.3, 134.0, 133.8, 129.1, 128.9, 125.1, 124.9, 111.0, 104.4, 97.4, 94.9, 62.3, 61.6, 47.6, 47.5, 23.7. hrms-maldi: m/z $[M+H]^+$ calcd for $C_{36}H_{26}N_6O_6S_4$: 767.08694, found : 767.08713.

7,8-Bis{[1-(4-benzoylbenzyl)-*1H*-1,2,3-triazol-4-yl]methoxy}-4-methyl-*2H*-chromen-2-one (14a). (0.68 g), 92 %, beige-brown solid, mp 117-119 °C. ^{1}H nmr (DMSO-d_6): δ 8.40 (s, 1H), 8.22 (s, 1H), 7.68-7.65 (m, 12H), 7.55-7.40 (m, 6H), 7.32-7.25 (m, 2H), 6.15 (s, 1H), 5.74 (s, 2H, NCH_2), 5.69 (s, 2H, NCH_2), 5.31 (s, 2H, OCH_2), 5.16 (s, 2H, OCH_2), 2.49 (s, 3H, CH_3). ^{13}C nmr (DMSO-d_6): δ 195.2, 159.4, 153.8, 153.3, 147.3, 140.5, 140.4, 136.9, 136.8, 136.6, 136.5, 133.6, 132.7, 130.1, 130.0, 129.5, 128.5, 127.8, 127.5, 125.2, 125.1, 120.5, 114.2, 111.6, 110.2, 65.4, 62.3, 52.3, 52.2, 18.1. hrms-maldi: m/z $[M+H]^+$ calcd for $C_{44}H_{34}N_6O_6$: 743.26126, found : 743.26120.

7,8-Bis({1-[(5-benzoyl-2-thienyl)methyl]-*1H*-1,2,3-triazol-4-yl}methoxy)-4-methyl-*2H*-chromen-2-one (14b). (0.40 g), 53 %, beige-brown solid, mp 135-137 °C. ^{1}H nmr (DMSO-d_6): δ 8.41 (s, 1H), 8.23 (s, 1H), 7.80-7.76 (m, 4H), 7.67-7.59 (m, 2H), 7.57-7.7.45 (m, 7H), 7.30-7.25 (m, 2H), 7.20-7.16 (m, 1H), 6.16 (s, 1H), 5.95 (s, 2H, NCH_2), 5.88 (s, 2H, NCH_2), 5.31 (s, 2H, OCH_2), 5.15 (s, 2H, OCH_2), 2.34 (s, 3H, CH_3). ^{13}C nmr (DMSO-d_6): δ 187.1, 159.4, 153.8, 153.3, 147.3, 147.1, 147.0, 143.1, 142.9, 142.7, 137.0, 135.4, 133.5, 132.6, 129.0, 128.8, 128.6, 124.9, 120.5, 114.4, 111.5, 110.2, 65.7, 62.5, 47.7, 47.5, 30.7, 18.1. hrms-maldi: m/z $[M+H]^+$ calcd for $C_{40}H_{30}N_6O_6S_2$: 755.17410, found : 755.17410.

4-Methyl-7,8-bis({1-[4-(2-thienylcarbonyl) benzyl]-*1H*-1,2,3-triazol-4-yl}methoxy)-*2H*-chromen-2-one (14c). (0.67 g), 89 %, yellow-orange solid, mp 120-121 °C. ^{1}H nmr (DMSO-d_6): δ 8.40 (s, 1H), 8.23 (s, 1H), 8.11-8.09 (m, 2H), 7.82-7.76 (m, 4H), 7.67 (d, 2H, J=3.8 Hz), 7.48-7.41 (m, 3H), 7.33-7.23 (m, 6H), 6.17 (s, 1H), 5.75 (s, 2H, NCH_2), 5.68 (s, 2H, NCH_2), 5.32 (s, 2H, OCH_2), 5.16 (s, 2H, OCH_2), 2.35 (s, 3H, CH_3). ^{13}C nmr (DMSO-d_6): δ 186.8, 159.5, 153,8, 153.3, 147.3, 142.5, 140.4, 140.3, 137.1, 137.0, 135.8, 135.6, 133.6, 129.3, 129.2, 128.8, 127.9, 127.7, 125.2, 120.5, 114.4, 111.6, 110.3, 65.4, 62.3, 52.4, 52.2, 18.1. hrms-maldi: m/z $[M+H]^+$ calcd for $C_{40}H_{30}N_6O_6S_2$: 755.17410, found : 755.17411.

4-Methyl-7,8-bis[(1-{[5-(2-thienylcarbonyl)-2-thienyl]-methyl}-*1H*-1,2,3-triazol-4-yl)methoxy]-*2H*-chromen-2-one (14d). (0.73 g), 95 %, pink-brown solid, mp 190-191 °C. ^{1}H nmr (DMSO-d_6): δ 8.41 (s, 1H), 8.22 (s, 1H), 8.09 (dt, 2H, J=5.0, 2.7 Hz), 8.00 (dd, 2H, J=3.9, 1.1 Hz), 7.93-7.88 (m, 2H), 7.43 (d, 1H, J=8.9 Hz), 7.30-7.18 (m, 5H), 6.15 (d, 1H, J=1.2 Hz), 5.95 (s, 2H, NCH_2), 5.87 (s, 2H, NCH_2), 5.31 (s, 2H, OCH_2), 5.16 (s, 2H, OCH_2), 2.33 (s, 3H, CH_3). ^{13}C nmr (DMSO-d_6): δ 177.7, 159.6, 153.8, 153.3, 147.4, 146.4, 146.3, 142.4, 142.3, 141.6, 141.5, 135.2, 134.0, 133.8, 133.7, 133.5, 129.0, 128.9, 128.8, 124.9, 120.5, 114.4, 111.5, 110.3, 65.7, 62.1, 47.4, 47.3, 18.1. hrms-maldi: m/z $[M+H]^+$ calcd for $C_{36}H_{26}N_6O_6S_4$: 767.08694, found : 767.08662.

General procedure for the preparation of compounds 15 (a-d). Compounds **15a-d** were obtained from 2-(2-Oxo-*2H*-benzo[*h*]chromen-4-yl)-N-(2-propyn-yl)acetamide **8**, using the same procedure as for **12a-d**.

***N*-{[1-(4-Benzoylbenzyl)-1*H*-1,2,3-triazol-4-yl]methyl}-2-(2-oxo-*2H*-benzo[*h*]chromen-4-yl) acetamide (15a).** (0.49 g), 92 %, beige-brown solid, mp 165-168 °C. ^{1}H nmr (DMSO-d_6): δ 8.81 (t, 1H, N*H*, J=5.3 Hz), 8.36-8.32 (m, 1H), 8.01-7.97 (m, 2H), 7.80-7.66 (m, 9H), 7.57-7.51 (m, 2H), 7.40 (d, 2H, J=8.1 Hz), 6.55 (s, 1H), 5.68 (s, 2H, NCH_2), 4.34 (d, 2H, NHCH_2, J=5.4 Hz), 3.86 (s, 2H, COCH_2). ^{13}C nmr (DMSO-d_6): δ 195.2, 167.6, 159.6, 151.6, 149.9, 140.5, 136.8, 136.6, 134.2, 132.7, 130.0, 129.6, 128.6, 128.5, 127.8, 127.4, 123.8, 122.2, 121.5, 121.2, 115.7, 114.7, 52.2, 34.6, 33.2. hrms-maldi: m/z $[M+H]^+$ calcd for $C_{32}H_{24}N_4O_4$: 529.18703, found : 529.18699.

***N*-({1-[(5-Benzoyl-2-thienyl)methyl]-1*H*-1,2,3-triazol-4-yl}-methyl)-2-(2-oxo-*2H*-benzo[*h*]chromen-4-yl)acetamide (15b).** (0.51 g), 96 %, pale yellow solid, mp 142-145 °C. ^{1}H nmr (DMSO-d_6): δ 8.81 (t, 1H, N*H*, J=5.3 Hz), 8.38-8.34 (m, 1H), 8.04-7.98 (m, 2H), 7.81-7.76 (m, 3H), 7.73-7.67 (m, 4H), 7.58-7.53 (m, 3H), 7.21 (d, 1H, J=3.9 Hz), 6.55 (s, 1H), 5.89 (s, 2H, NCH_2), 4.33 (d, 2H, NHCH_2, J=5.2 Hz), 3.86 (s, 2H, COCH_2). ^{13}C nmr (DMSO-d_6): δ 187.1, 167.6, 159.5, 151.6, 149.9, 147.2, 142.9, 137.0, 135.4, 134.2, 132.6, 128.9, 128.8, 128.7, 127.9, 127.4, 123.8, 122.2, 121.5, 121.2, 115.7, 114.7, 47.4, 34.4, 33.4. hrms-maldi: m/z $[M+H]^+$ calcd for $C_{30}H_{22}N_4O_4S$: 535.14345, found : 535.14352.

2-(2-Oxo-*2H*-benzo[*h*]chromen-4-yl)-N-({1-[4-(2-thienyl-carbonyl)benzyl]-*1H*-1,2,3-triazol-4-yl}methyl)acetamide (15c). (0.52 g), 97 %, pale yellow solid, mp 196-199 °C. ^{1}H nmr (DMSO-d_6): δ 8.81 (t, 1H, N*H*, J=5.3 Hz), 8.37-8.33 (m, 1H), 8.12 (dd, 1H, J=4.9, 0.8 Hz) 8.02-7.98 (m, 2H), 7.81-7.67 (m, 7H), 7.41 (d, 2H, J=8.1 Hz), 7.27 (dd, 1H, J=4.8, 3.9 Hz), 6.55 (s, 1H), 5.68 (s, 2H, NCH_2), 4.34 (d, 2H, NHCH_2, J=5.3 Hz), 3.86 (s, 2H, COCH_2). ^{13}C nmr (DMSO-d_6): δ 186.8, 167.6, 159.6, 151.6, 149.9, 142.5, 140.4, 137.1, 135.8, 135.6, 134.2, 129.2, 128.8, 128.7, 127.9, 127.8, 127.5, 123.8, 122.2, 121.5, 121.2, 115.7, 114.7, 52.2, 34.4. hrms-maldi: m/z $[M+H]^+$ calcd for $C_{30}H_{22}N_4O_4S$: 535.14345, found : 535.14343.

2-(2-Oxo-*2H*-benzo[*h*]chromen-4-yl)-N-[(1-{[5-(2-thienyl-carbonyl)-2-thienyl]methyl}-*1H*-1,2,3-triazol-4-yl)methyl]-acetamide (15d). (0.35 g), 65 %, pale yellow solid mp 136-139 °C. ^{1}H nmr (DMSO-d_6): δ 8.81 (t, 1H, N*H*, J=5.3 Hz), 8.38-8.34 (m, 1H), 8.10 (d, 1Hμ, J=4.1 Hz) 8.04-8.00 (m, 3H), 7.89 (d, 1H, J=3.8 Hz), 7.80-7.67 (m, 4H), 7.31-7.28 (m, 1H), 7.24 (d, 1H, J=3.8 Hz), 6.55 (s, 1H), 5.859 (s, 2H, NCH_2), 4.33 (d, 2H, NHCH_2, J=4.6 Hz), 3.86 (s, 2H, COCH_2). ^{13}C nmr (DMSO-d_6): δ 177.7, 167.6, 159.5, 151.6, 149.9, 149.8, 146.6, 142.3, 141.6, 135.3, 134.2, 134.0, 133.8, 128.9, 128.8, 128.7, 127.9, 127.4, 123.8, 122.2, 121.5, 121.2, 115.7, 114.7, 47.5, 34.5. hrms-maldi:

m/z $[M+H]^+$ calcd for $C_{28}H_{20}N_4O_4S_2$: 541.09987, found : 541.09993.

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REFERENCES

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[1] (a) Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry* Pawda, A. Ed.; Wiley, New York, 1984; Vol 1, pp 1-176. (b) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565. (c) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 633.

[2] Kolb, H. C.; Finn, M. G.; Sharples, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

[3] Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

[4] Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.***2004**, *126,* 15046.

[5] Arosio, D.; Bertoli, M.; Manzonib, L.; Scolasticoa, C. *Tetrahedron Lett.* **2006**, *47*, 3697.

[6] Kosiova, I.; Kovackova, S.; Kois, P. *Tetrahedron* **2007**, *63*, 312.

[7] Natala, S. R., Muralidhar, R. M., Stephen, C.; Kiranmai G.; Stanley C. B.; Premkumar, R.; Ramana, M. V. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4093.

[8] (a) Yang, Z.-Y.; Xia, Y.; Xia, P.; Cosentino, L. M.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1483. (b) Spino, C.; Dodier, M.; Sotheeswaran, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3475. (c) Bedoya, L. M.; Beltrán, M.; Sancho, R.; Olmedo, D. A.; Sánchez-Palomino, S.; del Olmo, E.; López-Pérez, J. L.; Muñoz, E.; San Feliciano, A.; Alcamí, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4447.

[9] (a) Khan, I. A.; Kulkarni, M. V.; Sun, C.-M. *Eur. J. Med. Chem.* **2005**, *40*, 1168. (b) Bonsignore, L.; Cottiglia, F.; Elkhaili, H.; Jehl, F.; Lavagna, S. M.; Loy, G.; Manna, F.; Monteil, H.; Pompei, D.; Secci, D. *Il Farmaco* **1998**, *53*, 425.

[10] (a) Manolov, I.; Danchev, N. *Eur. J. Med. Chem.* **1995**, *30*, 531. (b) Manolov, I.; Maichle-Moessmer, C.; Danchev, N. *Eur. J. Med. Chem.* **2006**, ***41,*** 882.

[11] Bariana, D. S. *J. Med. Chem.* **1970**, *13,* 544.

[12] (a) Ghate, M.; Kusanur, R. A.; Kulkarni, M. V. *Eur. J. Med. Chem.* **2005**, *40*, 882. (b) Ghate, M.; Manohar, D.; Kulkarni, V.; Shobha, R.; Kattimani, S. Y. *Eur. J. Med. Chem.* **2003**, *38*, 297. (c) Kontogiorgis, C. A.; Hadjipavlou-Litina, D. J. *J. Med. Chem.* **2005**, *48*, 6400.

[13] (a) Beillerot, A.; Rodríguez Domínguez, J. C.; Kirsch, G.; Bagrel, D. *Bioorg. Med. Chem. Lett.* **2008**, in press. (b) Tyagi, Y. K.; Kumar, A.; Raj, H. G.; Vohra, P.; Gupta, G.; Kumari, R.; Kumar, P.; Gupta, R. K. *Eur. J. Med. Chem.* **2005**, *40*, 413.

[14] (a) Peng, F.-C.; Cheng, J.-S. Mycopathologia 1997, 137, 125. (b) Garino, C.; Pietrancosta, N.; Laras, Y.; Moret, V.; Rolland, A.; Quéléver, G.; Kraus, J.-L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1995. (c) Cravotto, G.; Balliano, G.; Robaldo, B.; Oliaro-Bosso, S.; Chimichib, S.; Boccalini, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1931. (d) Onderwater, R. C. A.; Venhorst, J.; Commandeur, J. N. M.; Vermeulen, N. P. E. *Chem. Res. Toxicol.* **1999**, *12*, 555. (e) Laurin, P.; Ferroud, D.; Klich, M.; Dupuis-Hamelin, C.; Mauvais, P.; Lassaigne, P.; Bonnefoy, A.; Musicki, B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2079.

[15] Seela, F.; Sirivolu, V. R.; Chittepu, P. *Bioconjugate Chem.* **2008,** *19,* 211.

[16] (a) Kosiova, I.; Kovackova, S.; Kois, P. *Tetrahedron* **2007**, *63*, 312. (b) Nonaka, H.; Tsukiji, S.; Ojida, A.; Hamachi, I. *J. Am. Chem. Soc.* **2007**, *129*, 15777.

[17] (a) Beatty, K. E.; Xie, F.; Wang, Q.; Tirrell, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 14150. (b) Gierlich, J.; Burley, G. A.; Gramlich, P. M. E.; Hammond, D. H.; Carell, T. *Org. Lett.* **2006**, *8*, 3639. (c) Jawalekar, A. M.; Cremers Meeuwenoord, N. J. (S.) G. O.; Overkleeft, H. S. Van der Marel, G. S.; Rutjes, F. P. J. T.; Van Delft, F. L. *J. Org. Chem.* **2008**, *73*, 287. (d) Haensch, C.; Hoeppener, S.; Schubert, U. S. *Nanotechnology* 2008, *19*, 035703 (7pp). (e) Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q. *Org. Lett.* **2004**, 6, 4603. (f) Zhou, Z.; Fahrni, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 8862.

[18] (a) Bernardi, D.; Ba, L.A.; Kirsch, G. *Synthesis* **2007**, 140. (b) Bernardi, D.; Battaglia, E.; Kirsch, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1601. (c) Bernardi, D.; Dicko, A.; Kirsch, G. *Synthesis* **2006**, 509.

[19] Dorman, G.; Prestwich, G. D. *Biochemistry* **1994**, *33*, 5661.

[20] Singh, A.; Thornton, E. R.; Westheimer, F. H. *J. Biol. Chem.* **1962**, *237*, PC3006.

[21] (a) Rodríguez-Domínguez, J. C.; Kirsch, G. *Synthesis* **2006**, 1895. (b) Rodríguez-Domínguez, J. C.; Kirsch, G. *Tetrahedron Lett.* **2006**, 47, 3279.

[22] (a) Hatano, B.; Kadokawa, J.; Tagaya, H. *Tetrahedron Lett.* **2002**, *43*, 5859. (b) Wang, D.; Zhang, Z. *Org. Lett* **2003**, *5,* 4645. (c) Repichet, S.; Le Roux, C.; Roquesb, N.; Dubaca, J. *Tetrahedron Lett.* **2003**, *44*, 2037. (d) Urawaa, Y.; Ogurab, K. *Tetrahedron Lett.* **2003**, *44*, 271. (e) Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534. (f) Kan, T.; Tominari, Y.; Rikimaru, K.; Morohashi, Y.; Natsugari, H.; Tomita, T.; Iwatsubo, T.; Fukuyama, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1983. (g) Sarvari, M. H.; Sharghi, H. *J. Org. Chem.* **2004**, *69*, 6953. (h) Matsushita, Y.; Sugamoto, K.; Matsui, T. *Tetrahedron Lett.* **2004**, *45*, 4723. (i) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302. (j) Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V.; Thanusu, J. *Catalysis Commun.* **2005**, *6*, 753. (k) Kang, O.; Luo, J.; Bai, Y.; Yang, Z.; Lei, Z. *J. Organomet. Chem.* **2005**, *690*, 6309.(l) Bandgar, B. P.; Patil, A. V. *Tetrahedron Lett.* **2005**, *46*, 7627. (m) Kangani, C. O.; Kelleya, D. E.; Day, B. W. *Tetrahedron Lett.* **2006**, *47*, 6289. (n) Xing, D.; Guan, B.; Cai, G.; Fang, Z.; Yang, L.; Shi, Z. *Org. Lett.* **2006**, *8*, 693. (o) Jang, D. O.; Moon, K. S.; Choa, D. H.; Kim, J.-G. *Tetrahedron Lett.* **2006**, *47*, 6063. (p) Xin, B.; Zhang, Y.; Cheng, K *J. Org. Chem.* **2006**, *71*, 5725.

[23] (a) Takeda, Y.; Kumazawa, T. *Bull. Chem. Soc. Japan*, **1988**, *61*, 455. (b) Kang, S.-K.; Ryu, H-C.; Lee, S-W. *J. Organomet. Chem.* **2000**, *610*, 38. (c) Rahman, O.; Kihlberg, T.; Langström, B. *Eur. J. Org. Chem.* **2004**, 474. (d) Katritzky, A. R.; Suzuki, K.; Singh, S. K. *Croatica Chemica Acta,* **2004**, *77*, 175. (e) De Martino, G.; La Regina, G.; Di Pasquali, A.; Ragno, R.; Bergamini, A.; Ciaprini, C.; Sinistro, A.; Maga, G.; Crespan, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2005**, *48*, 4378. (f) Rieke, R. D.; Suha, Y. S.; Kim, S.-H. *Tetrahedron Lett.* **2005**, *46*, 5961. (g) Polackova, V.; Toma, S.; Augustınova, I. *Tetrahedron* **2006**, *62*, 11675.

[24] (a) Futatsuya, F.; Yamane, N.; Ito, K.; Yamada, O.; Fujii, Y.; Ishida, S. German Patent 2,503,216, 1975; *Chem. Abstr.*, **1975**, *83*, 173933y. (b) Noto, R.; Gruttadauria, M.; LoMeo, P.; Spinelli, D. *Collection Czechoslovak Chem. Commun.* **1999**, *64*, 1893.

[25] Dey, B. B. *J. Chem. Soc., Trans.* **1915**, *107*, 1606.

[26] Rodighiero, P.; Manzini, P.; Pastorini, G.; Bordin, F.; Guiotto, A. *J. Heterocycl. Chem.* **1987**, *24*, 485.