SYNTHESIS AND REACTIONS OF SOME SPIROFUROCHROMANONE DERIVATIVES WITH POTENTIAL BIOLOGICAL ACTIVITY

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Abstract: *Condensation of differnet spiro furochromanone derivatives 1a-c with malononitrile afforded N(1'-cyanoethyl-2',2'-dicyanovinyl) chromen-5-amine 2a,b and the ylidene malononitrile 3a-c derivatives according to the reaction conditions. Reaction of the latter products with hydrazine hydrate phenyl hydrazine and thiourea gave the products 4-8. Reaction of the ylidene 3a-c with sulphur and triethylamine to give the product 9a-c. The latter were reacted with different aromatic aldehyde, acetic anhydride, diethylmalonate and dimethyl acetylenedicarboxylate to give the product 10-14.*

Introduction

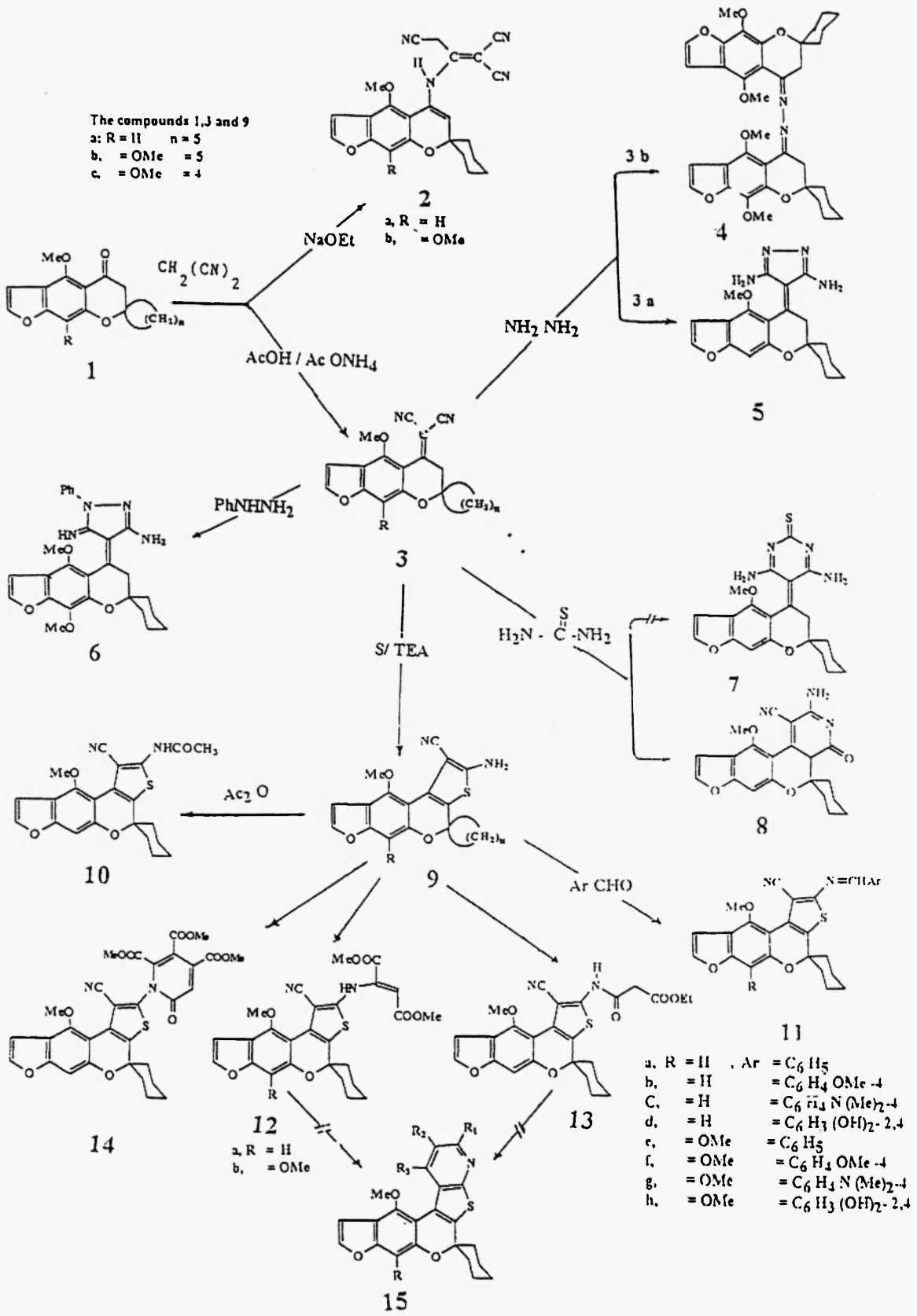
The naturally occurring furobenzopyran and benzofuran rings as the basic skeleton of nuemrous compounds possessing cardiovascular and antiarrhythmic activity (1-3). Benzopyranone used as sapasmolytic, cytotoxic and hepatotoxic and antidiabetic (4,5). Also, furochromone derivatives are used as antispamodics for the relief of spasms of the ureter, bile duct, gall bladder and bronchial asthma (6).

Chemistry and Discussion

Condensation of spirofurochromanones derivatives **1a** or **1b** (7) with malononitrile afforded two different products according to the reaction conditions, at using ethanolic sodium ethoxide solution gave spirocyclohexyl furochromen-5-amine derivatives **2a,b** via dimerization of malonitrile before its condensation in one pot reaction, whereas in acetic acid/ammonium acetate mixture afforded the ylidene malononitrile derivatives **3a-c**. ^{1}H NMR spectrum of compound **2b** showed clearly a singlets signals at δ = 3.54, 5.16 and 11.98 for CH_2, CH and NH protons respectively.

The ylidene malononitrile **3a,b** were reacted with hydrazine hydrate to afford the diylidene hydrazine **4** which probably from Michael addition to α,β unsaturated nitrile followed by extrusion malononitrile molecule. The same compound **4** cannot be obtained directly from reaction of **1b** with hydrazine hydrate. In another attempt, at room temperature the diamino pyrazole derivative **5** was separated. ^{1}H NMR spectra of the compounds **4** and **5** showed the methylene protons at δ = 3.1 and 2.6 ppm also a two amino groups was appeared as broad peaks at δ = 5.4 and 6.4 ppm.

The ylidene malononitrile **3b** reacted with phenyl hydrazine to give the corresponding furochroman-5-yl pyrazole derivatives **6**. Whereas refluxing a mixture of **3a** and thiourea in sodium ethoxide solution, the diaminopyrimidinthione derivative **7** not obtianed, instead compound **8**, was separated which clearly established from a characteristic cyano absorption band at ν = 2190.


The compounds 1,3 and 9
a: R = H n = 5
b, = OMe = 5
c, = OMe = 4
NaOEt
CH2(CN)2
AcOH / Ac ONH4
NH2 NH2
3 b
3 a
PhNHNH2
S/ TEA
H2N - C(=S) -NH2
Ac2 O
Ar CHO
1
2
a, R = H
b, = OMe
3
4
5
6
7
8
9
10
11
a, R = H , Ar = C6 H5
b, = H = C6 H4 OMe -4
C, = H = C6 H4 N (Me)2-4
d, = H = C6 H3 (OH)2- 2,4
e, = OMe = C6 H5
f, = OMe = C6 H4 OMe -4
g, = OMe = C6 H4 N (Me)2-4
h, = OMe = C6 H3 (OH)2- 2,4
12
a, R = H
b, = OMe
13
14
15

Also, at reaction of 3a-c with sulphur and triethylamine gave a quantitatively yield from the corresponding 6-amino-5-cyano-4-methoxy furo [3,2 g] thieno[2,3-c] chromen derivatives 9a-c. N-acylation of 9a yielded 6-acetamido-5-cyano-4-methoxy-7-pentamethylene furo[3,2-g]thieno[2,3-c]chromen 10, which showed in IR spectrum disappearance of NH_2 signals.

The above products 9a or 9b were condensed with benzaldehyde, p-anisaldehyde, P-N,N-dimethylbenzaldehyde and 2,4-dihydroxy benzaldehyde to give the corresponding products 11a-h. Also, reaction of 9a or 9b with dimethyl acetylene dicarboxylate and diethyl malonate in different basic medium, compound 15 not obtained instead, the compounds 12-14 were separated.

Experimental

All melting points are uncorrected. The IR spectra were recorded on a Mattson 500 FTTR spectrometer using in all sample KBr disk and elemental analyses were carried out in the Microanalytical Unit (Faculty of Science, Mansoura University). The ^1H NMR were recorded on Varian - Gemini 200 MHz using TMS as internal standard and $CDCl_3$ as solvent.

Reaction of malononitrile with compound 1a-c.

A: Preparation of N-(1'-cyanomethyl-2',2'-dicyanovinyl) 4-methoxy (and 4,9-dimethoxy)-7-pentamethylene furo[3,2-g]8H-Chromen-5-amine 2a and 2b.

A mixture of compound 1a or 1b (7) (10 mmol) and malononitrile (20 mmol) in absolute ethanol (30 ml) were refluxed with stirring. Sodium ethoxide solution (0.4 g in 10 ml absolute ethanol) was dropwisely added through 15 min then heating was continued for 5 hrs. The reaction mixture was poured into crushed ice after cooling and neutralized with diluted hydrochloric acid. The precipitate formed was filtered off, washed with water and crystallized from ethanol.

IR (compound 2a) ν = 3131 (NH), 2994, 2866(CH), 2219(C≡N) and 1624 cm^{-1}.

IR (Compound 2b) ν = 3100(NH), 2932, 2859(CH), 2220(C≡N) 1612(C=N), 1584(Ar.).

^1H NMR (Compound 2b) δ = 1.2- 2.1(m, 10H, five CH_2), 3.84(s, 2H, CH_2CN), 4.06(s, 3H, OCH_3), 4.18(s, 3H, OCH_3) 5.16(s, 1H, H-6), 6.92(d, 1H, H-3), 7.53(d, 1H, H-2), 11.98(s, 1H, NH).

B: Preparation of the ylidene malononitrile 3a-c "general procedure"

A mixture of compound **1a-c** (10 mmol), malononitirle (10 mmol), ammonium acetate (3 g) and acetic acid (3 ml) were refluxed in chloroform (200 ml) using dean stark apparatus for 8 hrs. The solvents were evaporated under vacuum then water (100 ml) was added. The precipitate formed was filtered off, washed with water and crystallized from ethanol

IR (Compound 3a) ν = 2931, 2853 (CH), 2209(C≡N) and 1613 cm^{-1}.

IR (Compound 3b) ν=2936, 2852 (CH),2224(C≡N) and1622 cm^{-1} (C=C).

IR (Compound 3c) ν=3131, 2950(CH), 2223(C≡N) and 1612 cm^{-1} (C=C).

Reaction of 3a,b with hydrazine hydrate

A: Preparation of di(4,9-dimethoxy-7-pentamethylene furo(3,2-g) chroman-5-ylidene) hydrazine (4)

A mixture of compound 3b (10 mmol) and hydrazine monohydrate (1 ml, 98%) was boiled in absolute ethanol for 6 hrs. The reaction mixture was evaporated and the residue was crystallized from ethanol.

IR ν = 2930, 2860(CH), 1616(C=N) and 1591 cm^{-1} (Ar).

^{1}H NMR δ = 1.5-2.4(m, 20H, Ten CH_2 groups), 3.11(s, 4H, Two CH_2), 4.02 (2s, 12H four OCH_3) 6.88(d, 2H, two H-3) and 7.5 ppm(d, 2H, H-2).

B: Preparation of 3,5-diamino-4(4`-methoxy-7'-pentamethylene-furo[3',2'-g].Chroman-5-ylidene)-4H-pyrazole 5

Hydrazine hydrate (1 ml, 98%) was added dropwise to a stirred solution of 2a (3.34 g 10 mol) in absolute ethanol through 10 min. The reaction mixture was stirred at room temperature with controlling the time of reaction using TLC for about 30 min. Then poured into crushed ice (30 g), filtered off and crystallized from ethanol.

IR ν = 3363, 3287, 3213, 3132 ($2NH_2$ groups), 2986, 1855(CH), 1620(C=N) and 1579 cm^{-1} (Ar.).

^{1}H NMR δ = 1.2-2.0(m, 10H, five CH_2), 2.57(s, 2H, H-6), 3.99(s, 3H, OMe), 5.15, 6.20(2s, broad, 4H, two NH_2 protons), 6.84(d, 1H, H-3) and 7.44 ppm(d, 1H, H-2).

Preparation of 1-phenyl-3-amino-4-(4,`,9-dimethoxy-7-pentamethylene furo[3",2"-g]chroman 5-ylidene)4H-pyrazole 6

A mixture of compound 3b (5 mmol) and phenyl hydrazine (6 mmol) in absolute ethanol was boiled under reflux for 5 hrs. The precipitate was formed after cooling, filtered off, washed with water, dried and crystallized from ethanol.

IR ν = 3360, 3218 (NH_2), 3210(NH), 1616(C=N) and 1591 cm^{-1} (Ar).

^{1}H NMR δ = 1.41-2.01(m, 10H, five CH_2), 2.66(s, 2H, H-6), 4.03, 4.10(2s, 6H, two OMe), 6.88(s, 2H, NH_2), 7.22(d, 1H, H-3), 7.25-7.33(m, 5H, Ar-H), 7.48(d, 1H, H-2).

Reaction of compound 3a with thiourea "preparation of compound 8"

Sodium ethoxide solution (0.3 g/10 ml absolute ethanol) was added with stirring to a mixture from compound 3a (1.67 g, 5 mmol) and thiourea (0.51 g, 8 mmol) in ethanol (30 ml). The mixture was boiled for 4 hrs, then poured into cooled water (100 ml) and neutralized with diluted hydrochloric acid. The precipitate was collected, filtered off and crystallized from ethanol.

IR ν = 3418, 3260, 3137 (OH, NH_2), 3380-3000(br., enolic OH), 2924, 2859 (CH), 2190(sharp

strong C≡N), 1660, (C=O) and, 1613 cm^{-1} (Ar).

Synthesis of the compound 9a-c

A solution of the ylidene malononitrile **3a-c** (10 mmol), sulfur metal (0.4 g, 12 mmol) in absolute ethanol (50 ml) was boiled with stirring. Triethylamine (2 ml) was dropwisely added then heat the mixture for 6 hrs. The reaction mixture was concentrated in vacuo and the residue formed was crystallized from ethanol.

IR (Compound **9a**) ν=3450, 3337, 3201(NH_2), 2933, 2859(CH), 2197 (C≡N) and 1619, cm^{-1} (Ar.)

^{1}H NMR δ = 1.26-2.20(m, 10H, five CH_2), 4.26(s, 3H, OCH_3), 4.85(s, br. 2H, NH_2), 6.88(s, 1H, H-10) 6.98(d, 1H, H-3) and 7.47 ppm (d, 1H, H-2).

MS: M^+ (m/z = 366).

IR (Compound **9b**) ν = 3410, 3320, 3210 (NH_2), 2936, 2847(CH) and 2201 cm^{-1} (C≡N).

IR (Compound **9c**) ν = 3410, 3240 (NH_2), 2205(C≡N) and 1612(Ar.).

Synthesis of 6-acetamido-5-cyano-4-methoxy-8-pentamethylene furo [3,2-g]thiano[2,3-c]8H Chromen (10)

A mixture of compound **9a** (1 g, 2.7 mmol) and acetic anhydride (0.4 ml, 4 mmol) was boiled in acetic acid (10 ml) for 8 hrs. The reaction mixture was poured into crushed ice and the precipitate formed was filtered off, washed with water and crystallized from ethanol.

IR ν = 3273(NH), 2930, (CH), 2211(C≡N) 1692(amide I), 1623(amide II) and 1585 cm^{-1} (Ar.).

Condensation of compound 8 with aromatic aldehydes, preparation of the compounds 11a-h "general procedure"

A mixture of compound **9a or 9b** (3 mmol), the corresponding aldehyde (3 mmol) and triethyl amine (0.5 ml) in ethanol (30 ml) was refluxed for a time 3-5 hrs. The precipitate formed after cooling was filtered off, dried and crystallized from ethanol.

IR (Compound **11a**) ν = 2930, 2860 (CH), 2220 (C≡N) and 1610 cm^{-1} (C=N).

IR (Compound **11b**) ν = 2935, 2854 (CH), 2222 (C≡N), 1600(C=N), 1566 (Ar).

IR (Compound **11c**) ν = 2927, 2856 (CH) 2210 (C≡N and 1618 cm^{-1}

IR (Compound **11d**) ν = 3500-3200(br, OH bonded), 3170, 3130 (OH free), 2933, 2847 (CH), 2220(C≡N), 1626(C=N) and 1603 cm^{-1} (Ar).

IR (Compound **11e**) ν = 2935, 2849(CH), 2210 (C≡N) and 1605 cm^{-1} (C=N).

IR (Compound **11f**) ν = 2935, 2843(CH), 2216(C≡N), 1591(C=N) and 1566 cm^{-1}(Ar.)

IR (Compound **11g**) ν = 2932, 2840 (CH), 1613(C=N), 1578 (Ar.) 1533(Sh. strong $N(Me)_2$)

^{1}H NMR (Compound **11g**) δ = 1.25-2.1(m, 10H, five CH_2), 3.09(s, 6H, $N(CH_3)_2$), 4.1(s, 3H, OCH_3), 4.22(s, 3H, OCH_3), 6.71(d, 2H, J = 45 Hz Two H-3'), 7.02(d, 1H, J = 11 Hz H-3), 7.52(d,

1H, J = 11Hz H-2), 7.86(d, 2H J = 45 Hz, Two H-2') and 8.37 ppm (s, 1H, N=CH).

IR (Compound **11h**) ν = 3600-3100(br., OH), 2935, 2858(CH), 2220 (C=N), 1619(C=N), 1600, 1574 (Ar.).

Reaction of compound 7 with dimethyl acetylenedicarboxylate or diethylmalonate

Preparation of the compounds 12-13 "General procedure"

Sodium ethoxide solution (0.5 g in 10 ml absolute ethanol) was dropwisely added to a mixture from compound **9a** or **9b** (10 mmol) and dimethyl acetylenedicarboxylate (or diethylmalonate) (12 mmol) in absolute ethanol (50 ml). The mixture was refluxed with stirring for 8 hrs, cooled, poured into crushed ice and neutralized with diluted hydrochloric acid. The precipitate formed was filtered off and crystallized from ethanol.

IR (Compound **12a**) ν = 2937, 2857(CH), 2220 (C≡N), 1736($COOCH_3$) and 1621 cm^{-1} (C=C).

IR (Compound **12b**) ν = 2220(C≡N), 1731($COOCH_3$), 1610(C=C) 1560(Ar)

IR (Compound **13**) ν = 3236 (NH), 3115, 2930, 2856(CH), 2221 (C≡N), 1730(COOEt), 1668 (amide I), 1624 (amide II) and 1583 cm^{-1} (Ar.)

^{1}H NMR (Compond **13**) δ = 1.35(t, 3H, CH_3CH_2), 1.41-2.17(m, 10H, five CH_2), 3.62(s, 3H, OCH_3), 4.28(s, 2H, $COCH_2CO$), 4.33(q, 2H, CH_3CH_2), 6.90(s, 1H, H-10), 7.01(d, 1H, H-3), 7.47(d, 1H, H-2), 10.95(s, 1H, amide NH).

Preparation of compound 14

A mixture from compound **9** (1.8 g, 5 mmol), dimethyl acetylene dicarboxylate (2.1 g, 15 mmol) and unhydrous potassium carbonate (1 g) in dimethyl sulphoxide (20 ml) was refluxed for 5 hrs. The reaction mixture was worked up as previously discussed in preparation of the compounds **12-13** to give compound **14** as pale yellow crystals.

IR ν = 2941, 2855(CH), 2220(C≡N), 1740 (COOMe) and 1700 cm^{-1} (C=O).

^{1}H NMR δ = 1.25-2.35(m, 10H, five CH_2), 3.70, 3.83, 3.93 (3 singlets, 9H, Three $COOCH_3$), 4.27(s, 3H, OCH_3) 6.93(s, 1H, CH of pyridone), 7.01 (d, 1H, J = 12 Hz H-3) and 7.50 ppm (d, 1H J = 12 Hz, H-2).

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Table 1 Characterization data of the new prepared compounds

Comp. No	M.P.°C	Yield %	Mol. formula mol.weight)	Analysis					
				Calcd.			Found		
				C	H	N	C	H	N
2a	126-28	81	$C_{23}H_{20}N_4O_3$(400.44)	69.00	5.03	14.00	69.16	5.22	13.78
2b	105-8	80	$C_{24}H_{22}N_4O_4$(430.46)	66.97	5.15	13.02	66.85	5.34	13.28
3a	125-27	93	$C_{20}H_{18}N_2O_3$(334.37)	71.84	5.34	8.38	71.69	5.61	8.18
3b	134-36	95	$C_{21}H_{20}N_2O_4$(364.40)	69.22	5.53	7.68	69.41	5.47	7.82
3c	127-29	85	$C_{20}H_{18}N_2O_4$(350.37)	68.56	5.18	8.00	68.70	5.35	7.99
4	197-99	80	$C_{36}H_{40}N_2O_8$(628.72)	68.77	6.41	4.46	68.91	6.61	4.37
5	214-18	82	$C_{20}H_{22}N_4O_3$(366.42)	65.56	6.05	15.29	65.44	6.23	15.08
6	178-80	90	$C_{27}H_{28}N_4O_4$(472.54)	68.53	5.97	11.85	68.37	5.79	11.94
8	215-17	76	$C_{21}H_{19}N_3O_4$(377.40)	66.83	5.07	11.13	66.68	5.24	11.08
9a	212-14	90	$C_{20}H_{18}N_2O_3S$(366.43)	65.56	4.95	7.64	65.80	4.81	7.79
9b	160-63	88	$C_{21}H_{20}N_2O_4S$(396.46)	63.61	5.08	7.06	63.42	5.26	7.22
9c	>300	78	$C_{20}H_{18}N_2O_4S$(382.43)	62.81	4.74	7.33	62.72	4.89	7.41
10	230-32	76	$C_{23}H_{22}N_2O_5S$(438.50)	63.00	5.06	6.39	63.17	5.21	6.14
11a	205-8	85	$C_{27}H_{22}N_2O_3S$(454.54)	71.35	4.88	6.16	71.58	4.97	6.01
11b	234-37	90	$C_{28}H_{24}N_2O_4S$(484.57)	69.40	4.99	5.78	69.28	4.79	5.91
11c	268-70	90	$C_{29}H_{27}N_3O_3S$(497.61)	70.00	5.47	8.44	70.17	5.32	8.32
11d	268.70	93	$C_{27}H_{22}N_2O_5S$(486.54)	66.65	4.56	5.76	66.80	4.77	5.91
11e	228-31	90	$C_{28}H_{24}N_2O_4S$(484.57)	69.40	4.99	5.78	69.28	4.69	5.53
11f	240-42	95	$C_{29}H_{26}N_2O_5S$(514.59)	67.69	5.09	5.44	76.69	5.31	5.28
11g	248-50	88	$C_{30}H_{29}N_3O_4S$(527.64)	68.29	5.54	7.96	68.08	5.29	7.77
11h	>300	85	$C_{28}H_{24}N_2O_6S$(516.57)	65.10	4.68.	5.42	65.31	4.75	5.29
12a	190-92	85	$C_{26}H_{24}N_2O_7S$(508.54)	61.41	4.76	5.51	61.66	4.58	5.80
12b	230-33	78	$C_{27}H_{26}N_2O_8S$(538.57)	60.21	4.87	5.20	60.19	4.72	5.43
13a	154-56	83	$C_{25}H_{24}N_2O_6S$(480.53)	62.49	5.03	5.83	62.34	5.28	5.71
15	182-84	75	$C_{31}H_{26}N_2O_{10}S$(618.61)	60.19	4.24	4.53	60.03	4.43	4.39