Convenient Synthesis of Some 2-Substituted 4(3*H*)-Quinazolinone Derivatives

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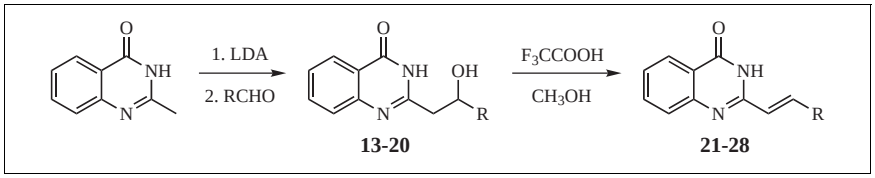

A series of 2-substituted-4(3*H*)-quinazolinones **13-20** has been synthesized in good yields using the reaction of double lithiated 2-methylquinazolinone-4 with a variety of aromatic aldehydes. They have been easily transformed in high yields into the corresponding 2-substituted conjugated derivatives **21-28** bearing terminal aryl groups by F_3CCOOH mediated dehydration.

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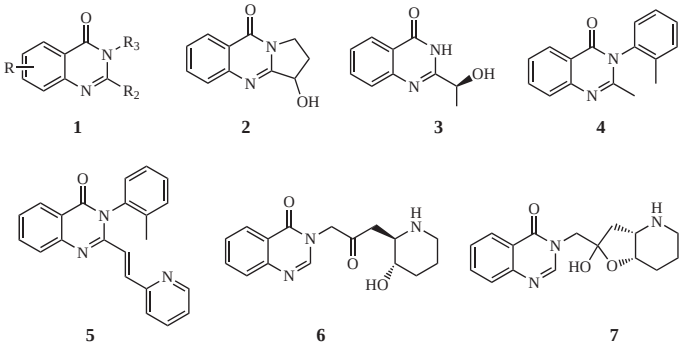
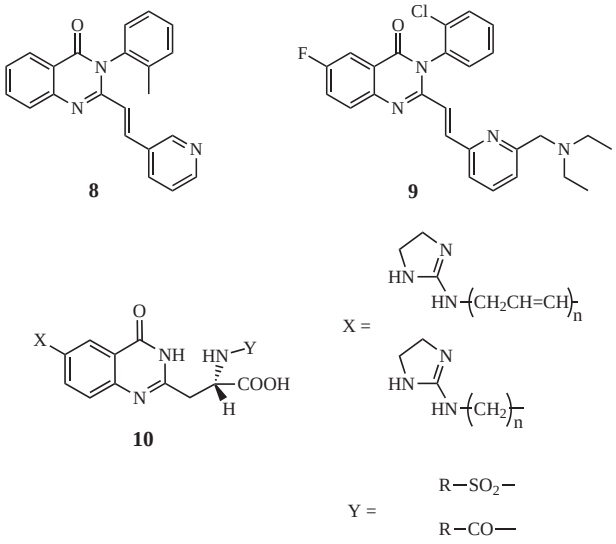
Introduction.

4(3*H*)-Quinazolinones **1** are known for more than a century [1]. Molecules based on quinazoline and quinazolinone exhibit a multitude of interesting pharmacological activities [2], including anticonvulsant, antibacterial and antidiabetic activity [3,4]. The important natural and synthetic 4(3*H*)-quinazolinones include *l*-vasicinone **2** [5], chrysogine **3** [6], methaquinalon **4** [7] – a sedative, piriqualone **5** [8,9] – an anticonvulsant, although the latter type of activity does not seem confined to pyridine derivatives of 4(3*H*)-quinazolinone [10]. Febrifugine **6** and isofebrifugine **7** were known as potent but toxic antimalarial agents long before their initial isolation [11] and recent chemical studies [12-15].



The most common synthetic approach to 2-substituted 3*H*-quinazolin-4-ones is based on acylation of anthranilic acid (or derivatives, *e.g.* 2-aminobenzonitrile) followed by cyclization and usually proceeds *via* an *o*-amidobenzamide intermediate [16-20]. Although there are numerous methods for the construction of the quinazolinone skeleton [21], only a few procedures for the synthesis of 2-vinyl derivatives of 3*H*-quinazolin-4-ones have been reported [22-24]. Several 2-styrylquinazolin-4(3*H*)-ones have been prepared since 1910 [24] and are active against certain types of cancer [4]. Pyridylvinyl-4(3*H*)-quinazolinones **8** showed anticonvulsant, hypnotic, tranquilizing and muscle relaxant activity. Their preparation occurs in two steps – condensation of 2-methyl-3,1-benzoxazin-4-one with 3-pyridine carboxaldehyde, followed by reaction with *o*-toluidine [26]. The atropisomers, 2-(2-heteroarylvinyl)-3-aryl-6-fluoro-4(3*H*)-quinazolinone **9**, known as AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonists [9], have been prepared using different synthetic procedures [27-31]. 2,6-Disubstituted 4(3*H*)-quinazolinones **10** are known as transmembrane receptor antagonists and their activity has been subjected to extensive molecular modeling [32]. Recent modeling and Quantitative Structure-Activity Relationships (QSAR) studies include quinazolinone inhibitors of poly(ADP-ribose) polymerase [33,34], indicating that quinazolinone drug design is rapidly approaching pre-clinical stage.



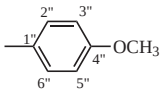
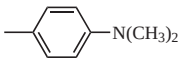
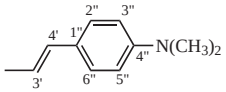
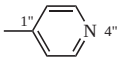
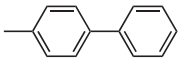
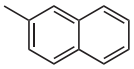
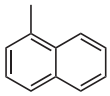
Derivatives of quinazoline and quinazolin-4-one are among the relatively less known dyes and pigments [35] and apparently no interest has been shown in their potential application in the nonlinear optics. As a part of our search program for suitable quinazolinone derivatives with promising classical and nonlinear optical properties like fluorescence and high (hyper) polarizabilities, we synthesized a series of 2-substituted 4(3*H*)-quinazolinones, experimentally registered their fluorescence spectra, and calculated theoretically the corresponding electrooptical properties [36].

reagent **12**, with no nucleophilic attack of LDA at either the carbonyl group or the imine group of the quinazolinone ring. The addition of LDA yielded a deep red solution, presumably due to formation of the anion of **12**. The mixture was allowed to stir at -78 °C for 1 h to ensure complete reaction.

The reaction of the anion **12** with a range of electrophiles, such as 4-methoxybenzaldehyde, 4-(dimethylamino)benzaldehyde, (*E*)-3-(4'-dimethylaminophenyl)acrylaldehyde, 3-pyridinecarboxldehyde, 4-pyridinecarboxaldehyde, biphenyl-4-carbaldehyde, 2-naphthaldehyde, 1-naphthaldehyde,

Table 1

Preparation of alcohols **13-20** according to Scheme 1.

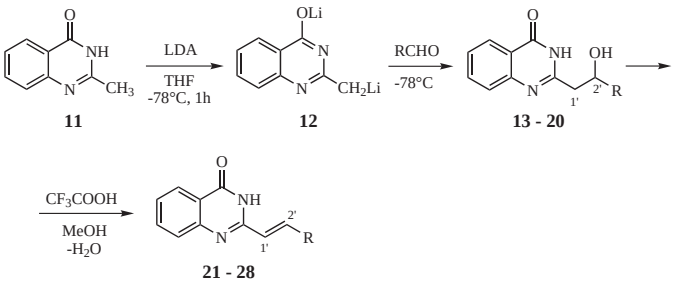
Entry	Aldehyde RCHO, R =	Product	Yield, %
1		**13**	58
2		**14**	56
3		**15**	50
4		**16**	55
5		**17**	64
6		**18**	81
7		**19**	73
8		**20**	72

In the present paper we describe a convenient route for the preparation of several 2-substituted 4(3*H*)-quinazolinones from 2-methyl-4(3*H*)-quinazolin-4-one, as mentioned earlier [36].

Results and Discussion.

Previously it has been shown that double lithiation of 3-unsubstituted 2-alkyl-4(3*H*)-quinazolinone is an useful method for side chain modification providing access to a broad variety of 2-substituted derivatives [37,38]. A series of 2-(2-hydroxy-2-arylethyl)-4-(3*H*)-quinazolinones (**13**–**20**) has been synthesized starting from 2-methyl-4(3*H*)-quinazolinone **11** (Scheme 1). As a lithiation agent LDA was chosen. Lithiation of **11** was achieved with 3 equivalents of LDA in THF at -78 °C to give a dilithio resulted in the formation of the corresponding 2-substituted-4(3*H*)-quinazolinones **13**–**20** (Scheme 1) in good yields within 2 h reaction time (Table 1).

Scheme 1



In all cases the obtained secondary alcohols were isolated in pure form by recrystallization from methanol. The structures of the compounds were confirmed by 1D and 2D NMR spectra and mass spectra as well as by elemental analysis. The synthesis of compound **13** by reaction of 2-methyl-4(3*H*)-quinazolinone **11** with *p*-methoxybenzaldehyde was reported previously but no NMR data were presented for this compound [37].

With the aim to obtain interesting quinazolinone derivatives with promising classical and nonlinear optical properties, a practical procedure has been optimized for the preparation of a series of 2-arylethylene and 2-aryl-butadienyl substituted 4-(3*H*)-quinazolinones [36].

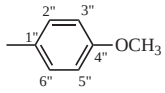
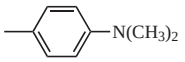
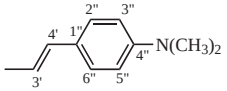
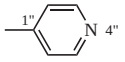
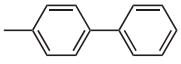
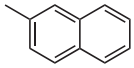
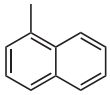
The dehydration of the secondary alcohols **13**–**20** was carried out in methanol under reflux using trifluoroacetic acid as a dehydration agent (Scheme 1). The corresponding 2-substituted aminoquinazolinone derivatives **21**–**28** were formed in high yields (Table 2). The reactions were relatively slow in the case of alcohols **13**, **16**-**20** (3h - 16h), whereas the dehydration of alcohols **14** and **15** (entries 2, 3) was completed within 15 min, as monitored by TLC. In all cases the corresponding 2-substituted 4-(3*H*)-quinazolinones have been isolated in pure form and their structures were identified by spectroscopic methods and elemental analysis. Because of the low solubility of some of the obtained products as a solvent for recording of NMR spectra a combination of $CDCl_3$ / CD_3OD/ CF_3COOD has been used. The dehydration of the secondary alcohols **13**–**20** in all cases led to the formation of the *trans*-isomers only. Preparation of compounds **21** and **22** has been reported recently by reaction of 2-methylquinazolinone-4 with the corresponding aromatic aldehydes in the presence of sodium acetate in acetic acid [24] but no NMR data for these products have been presented.

Conclusions.

We have demonstrated a practical method for the preparation of 2-substituted-4(3*H*)-quinazolinones (**13**–**20**), which can easily be transformed into 2-substituted conjugated derivatives (**21**–**28**) bearing terminal aryl groups. These compounds, **13**-**20**, as well as **21**-**28**, may possess biological activity, while the latter group indicates promising applications in nonlinear optics [36].

Table 2

Preparation of compounds **21**-**28** according to Scheme 1.

Entry	Starting alcohol	R	Product	Reaction time	Yield, %
1	**13**		**21**	3 h	95
2	**14**		**22**	15 min	92
3	**15**		**23**	15 min	94
4	**16**		**24**	16 h	75
5	**17**		**25**	16 h	72
6	**18**		**26**	16 h	96
7	**19**		**27**	6 h	88
8	**20**		**28**	6 h	87

Acknowledgement.

We wish to thank D.Sc. S. Simova and Dr. N. Vassilev from the Laboratory of Nuclear Magnetic Resonance for their assistance and helpful discussion.

EXPERIMENTAL

The reactions with organolithiums were carried out in Schlenk flasks under an argon atmosphere. THF was distilled over Na/benzophenone. Thin layer chromatography (TLC): aluminum sheets pre-coated with silica gel 60 F_{254} (Merck). Melting points of the compounds were determined using "Electrothermal" MEL-TEMP apparatus (uncorrected). The NMR spectra were recorded at ambient temperature (300 K) in DMSO-d_6 solutions, unless otherwise stated, on a *Bruker Avance DRX-250* spectrometer, operating at 250.13 and 62.90 MHz for ^{1}H NMR and ^{13}C NMR respectively, with TMS as internal standard for chemical shifts (δ, ppm). Mass spectra (MS) were recorded on a *Hewlett-Packard 5973A* spectrometer at 70 eV EI and are reported as fragmentation in *m/z* with relative intensities (%) in parentheses. Elemental analyses were performed by the Microanalytical service Laboratory of the Institute of Organic Chemistry, Bulgarian Academy of Science.

The following commercially available starting materials were used: 2-Methyl-4(3*H*)-quinazolinone hydrate (Aldrich), LDA 2M solution in THF/heptane/ethyl benzene (Fluka), 4-methoxybenzaldehyde (Aldrich), 4-(dimethylamino)benzaldehyde (Aldrich), (*E*)-3-(4'-dimethylaminophenyl)acrylaldehyde (Merck), 3-pyridinecarbaldehyde (Aldrich), 4-pyridinecarbaldehyde (Aldrich), biphenyl-4-carbaldehyde (Aldrich), 2-naphthaldehyde (Aldrich), 1-naphthaldehyde (Aldrich).

General Procedure for the Synthesis of 2-Substituted 4(3*H*)-Quinazolinone Derivatives **13-20**.

A 2 *M* solution of LDA (3.75 ml, 7.5 mmol) was added dropwise to a stirred solution of **11** (2.5 mmol) in anhydrous THF (25 ml) at -78 °C under argon atmosphere. Formation of the dianion was observed as a very deep red solution. The mixture was stirred at -78 °C for 1 h, after which an aldehyde (2.5 mmol) was added. The mixture was stirred for 2 h, then removed from the cooling bath and allowed to warm to room temperature and neutralized with aqueous saturated ammonium chloride solution and then with dilute HCl (2 *M* solution) till pH 6.5 – 7.0. The obtained precipitated solid was collected by filtration and recrystallized from methanol.

2-(2-Hydroxy-2-(4-methoxyphenyl)ethyl)quinazolin-4(3*H*)-one (**13**).

The compound was obtained as a colorless crystals, m.p. 180-181 °C (lit., [37] 177.5-179°C); ^{1}H-NMR: δ 2.89 (d, 2H, 1'-H, J = 6.6 Hz), 3.72 (s, 3H, H_3CO), 5.13 (dd, 1H, 2'-H, J = 6.6, 7.09 Hz), 6.89 (d, 2H, 3"-H, 5"-H, J = 8.8 Hz), 7.34 (d, 2H, 2"-H, 6"-H, J = 8.6 Hz), 7.43-7.49 (m, 1H, 6-H), 7.62 (d, 1H, 8-H, J = 7.6 Hz), 7.74-7.81 (m, 1H, 7-H), 8.08 (dd, 1H, 5-H, J = 0.9, 7.8 Hz), 12.17 (s, 1H, NH); ^{13}C-NMR: δ 44.9 (t, 1'-C), 55.0 (q, CH_3O), 70.4 (d, 2'-C), 113.5 (s, 3"-C, 5"-C), 120.9 (s, 4a-C), 125.7 (d, 8-C), 125.9 (d, 5-C), 126.8 (d, 6-C), 126.9 (d, 2"-C, 6"-C), 134.3 (d, 7-C), 137.0 (s, 1"-C), 148.9 (s, 8a-C), 155.5 (s, 2-C), 158.3 (s, 4"-C), 161.8 (s, 4-C); ms: m/z 296 (M^+, 4), 160 (M^+-$CH_3OC_6H_5CHO$, 100), 145 (12), 135 (82), 119 (17), 107 (14), 92 (26), 77 (27).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$ (296.32): C 68.91, H 5.44, N 9.45. Found: C 68.67, H 5.46, N 9.34.

2-(2-(4-(Dimethylamino)phenyl)-2-hydroxyethyl)quinazolin-4(3*H*)-one (**14**).

The compound was obtained as pale yellow crystals, m.p. 285-287°C; ^{1}H-NMR: δ 2.85-2.89 (m, 2H, 1'-H), 2.85 (s, 6H, $(CH_3)_2N$), 5.07 (t, 1H, 2'-H, J = 7.5 Hz), 6.69 (d, 2H, 2"-H, 6"-H, J = 8.8 Hz), 7.23 (d, 2H, 3"-H, 5"-H, J = 8.8 Hz), 7.42-7.49 (m, 1H, 6-H), 7.62 (d, 1H, 8-H, J = 7.8 Hz), 7.74-7.81 (m, 1H, 7-H), 8.08 (dd, 1H, 5-H, J = 1.5, 7.8 Hz); ^{13}C-NMR: δ 40.3 (q, $(CH_3)_2N$), 44.9 (t, 1'-C), 70.6 (d, 2'-C), 112.2 (d, 3"-C, 5"-C), 120.9 (s, 4a-C), 125.7 (d, 8-C), 125.9 (d, 5-C), 126.5 (d, 2"-C, 6"-C), 126.7 (d, 6-C), 132.6 (s, 1"-C), 134.3 (d, 7-C), 148.9 (s, 8a-C), 149.7 (s, (2-C), 155.7 (s, 4"-C), 161.8 (s, 4-C); ms: m/z 309 (M^+, 4), 291 (M^+-H_2O, 100), 276 (26), 262 (19), 160 (M^+-$(CH_3)_2NC_6H_5CHO$, 69), 148 (64), 120 (18), 92 (14), 77 (16).

Anal. Calcd. for $C_{18}H_{19}N_3O_2$ (309.36): C 69.88, H 6.19, N 13.58. Found: C 69.55, H 6.38, N 13.28.

2-(4-(4-(Dimethylamino)phenyl)-2-hydroxybut-3-enyl)quinazolin-4(3*H*)-one (**15**).

The compound was obtained as a pale yellow crystals, m.p. 172 °C; ^{1}H-NMR: δ 2.79-2.87 (m, 8H, $N(CH_3)_2$, 1'-H), 4.67 (dd, 1H, 2'-H, J = 6.4, 12.72 Hz), 6.36 (dd, 1H, 3'-H, J = 6.4, 15.9 Hz), 6.43 (d, 1H, 4'-H, J = 15.7 Hz), 6.64 (d, 2H, 2"-H, 6"-H, J = 8.8 Hz), 7.21 (d, 2H, 3"-H, 5"-H, J = 8.8 Hz), 7.41-7.47 (m, 1H, 6-H), 7.60 (d, 1H, 8-H, J = 8.3 Hz), 7.76 (ddd, 1H, 7-H, J = 1.5, 7.1, 8.1 Hz), 8.07 (dd, 1H, 5-H, J = 1.2, 7.8 Hz); ^{13}C-NMR: δ 40.2 (q, $N(CH_3)_2$), 43.3 (t, 1'-C), 70.3 (d, 2'-C), 112.5 (d, 3"-C, 5"-C), 121.1 (s, 4a-C), 124.8 (s, 1"-C), 125.9 (d, 8-C), 126.3 (d, 3'-C), 126.9 (d, 5-C), 127.5 (d, 2"-C, 6"-C), 127.9 (d, 6-C), 129.5 (d, 4'-C), 134.6 (d, 7-C), 149.1 (s, 8a-H), 150.2 (s, 4"-C), 155.8 (s, 2-C), 162.1 (s, 4-C); ms: m/z 335 (M^+, 6), 317 (M^+-H_2O, 100), 197 (68), 171 (24), 146 (6), 134 (60), 121 (16), 90 (6), 77 (6).

Anal. Calcd. for $C_{20}H_{21}N_3O_2$ (335.40): C 71.62, H 6.31, N 12.53. Found: C 71.36, H 6.45, N 12.46.

2-(2-Hydroxy-2-(pyridin-3-yl)ethyl)quinazolin-4(3*H*)-one (**16**).

The compound was obtained as colorless crystals, m.p. 185-186 °C; ^{1}H-NMR: δ 2.89-3.04 (m, 2H, 1'-H), 5.24 (dd, 1H, 2'-H, J = 6.12, 7.83 Hz), 5.74 (s, br., OH), 7.37 (dd, 1H, 3"-H, J = 4.6, 7.8 Hz), 7.43-7.50 (m, 1H, 6-H), 7.62 (d, 1H, 8-H, J = 7.8 Hz), 7.75-7.83 (m, 2H, 7-H, 4"-H), 8.08 (dd, 1H, 5-H, J = 1.5, 7.8 Hz), 8.46 (dd, 1H, 2"-H, J = 1.7, 4.6 Hz), 8.60 (d, 1H, 6"-H, J = 2.0 Hz), 12.19 (s, 1H, -NH); ^{13}C-NMR: δ 44.5 (t, 1'-C), 68.9 (d, 2'-C), 123.5 (d, 4"-C), 125.8 (d, 8-C), 126.2 (d, 5-C), 126.9 (d, 6-C), 133.7 (d, 3"-C), 134.5 (d, 7-C), 140.1 (s, 5"-C), 147.7 (d, 2"-C), 148.5 (d, 6"-C), 148.9 (s, 8a-C), 155.0 (s, 2-C), 161.9 (s, 4-C); ms: m/z 267 (M^+, 31), 248 (38), 160 (M^+-C_5H_3NCHO, 100), 145 (6), 132 (14), 120 (16), 108 (24), 92 (14), 77 (17).

Anal. Calcd. for $C_{15}H_{13}N_3O_2$ (267.28): C 67.40, H 4.90, N 15.72. Found: C 67.94, H 5.20, N 15.42.

2-(2-Hydroxy-2-(pyridin-4-yl)ethyl)quinazolin-4(3*H*)-one (**17**).

The compound was obtained as colorless crystals, m.p. 215-217 °C; ^{1}H-NMR: δ 2.84 (dd, 1H, 2'-H_b, J = 9.5, 13.9 Hz), 3.00 (dd, 1H, 2'-H_a, J = 4.2, 13.9 Hz), 2.89-3.04 (m, 2H, 1'-H), 5.19–5.22 (m, 1H, 2'-H), 5.82 (s, br., OH), 7.42 (d, 2H, 3"-H, 5"-H, J = 5.6 Hz), 7.44–7.50 (m, 1H, 6-H), 7.62 (d, 1H, 8-H, J = 8.1 Hz), 7.79 (ddd, 1H, 7-H, J = 1.2, 7.3, 8.1 Hz), 8.09 (d, 1H, 5-H, J = 7.1 Hz), 8.53 (d, 2H, 2"-H, 6"-H, J = 5.6 Hz), 12.24 (s, 1H,

-NH); ^{13}C-NMR: δ 44.0 (t, 1'-C), 69.4 (d, 2'-C), 120.8 (d, 3"-C, 5"-C), 125.6 (d, 8-C), 126.0 (d, 5-C), 126.7 (d, 6-C), 134.3 (d, 7-C), 148.7 (s, 4"-C), 149.4 (d, 6"-C, 2"-C), 153.4 (s, 8a-C), 154.7 (s, 2-C), 161.7 (s, 4-C); ms: m/z 267 (M^+, 38), 249 (50), 248 (45), 221 (8), 161 (19), 160 (100), 145 (10), 132 (14), 120 (20), 119 (25), 118 (15), 117 (10), 108 (12), 107 (31), 106 (13), 92 (19), 90 (19), 80 (13), 78 (18), 64 (10), 63 (11), 52 (11), 51 (19), 50 (13).

Anal. Calcd. for $C_{15}H_{13}N_3O_2$ (267.28): C 67.40, H 4.90, N 15.72. Found: C 67.15, H 4.93, N 15.48.

2-(2-(Biphenyl-4-yl)-2-hydroxyethyl)quinazolin-4(3*H*)-one (**18**).

The compound was obtained as colorless crystals, m.p. 201-202 °C; ^{1}H-NMR: δ 2.87–3.04 (m, 2H, 1'-H), 5.25 (dd, 1H, 2'-H, J = 4.6, 8.8 Hz), 7.31–7.37 (m, 1H, arom. proton), 7.42–7.54 (m, 5H, 6-H, 4 arom. protons), 7.63–7.66 (m, 5H, 7-H, 4 arom. protons), 7.79 (ddd, 1H, 7-H, J = 1.2, 7.1, 8.1 Hz), 8.11 (dd, 1H, 5-H, J = 1.2, 7.8 Hz); ^{13}C-NMR: δ 44.8 (t, 1'-C), 70.6 (d, 2"-C), 70.6 (d, 2"-C), 121.0 (s, 1 arom. C), 125.8 (d, 1 arom. C), 126.1, (d, 1 arom. C), 126.4, (d, 2 arom. C), 126.5 (d, 2 arom. C), 126.7 (d, 2 arom. C), 126.8 (d, 1arom. C), 127.4 (d, 1 arom. C), 129.0 (d, 2 arom. C), 134.4 (d, 1 arom. C), 139.0 (s, 1 arom.C), 140.0 (s, 1 arom.C), 144.2 (s, 1 arom.C), 148.9 (s, 8a-C), 155.5 (s, 2-C), 161.9 (s, 4-C); ms: m/z 342 (M^+, 10), 323 (19), 182 (100), 181 (97), 161 (14), 160 (95), 154 (16), 153 (51), 152 (67), 151 (22), 145 (12), 131 (9), 127 (9), 120 (13), 119 (19), 18 (17), 102 (7), 92 (17), 90 (17), 77 (19), 76 (23), 75 (10), 64 (10), 63 (15), 51 (9), 50 (10).

Anal. Calcd. for $C_{22}H_{18}N_2O_2$ (342.39): C 77.17, H 5.30, N 8.18. Found: C 77.08, H 5.42, N 8.12.

2-(2-Hydroxy-2-(naphthalen-2-yl)ethyl)quinazolin-4(3*H*)-one (**19**).

The compound was obtained as colorless crystals, m.p. 207-209 °C; ^{1}H-NMR: δ 2.91–3.08 (m, 2H, 1'-H), 5.33–5.38 (m, 1H, 2'-H), 5.72 (s, br., OH), 7.42–7.48 (m, 3H, 6-H, 2 arom. protons), 7.57–7.64 (m, 2H, 8-H, 1 arom. proton), 7.74–7.92 (m, 5H, 7-H, 4 arom. protons), 8.08 (d, 1H, 5-H, *J* = 7.6 Hz), 12.22 (s, 1H, -NH); ^{13}C-NMR: δ 44.8 (t, 1'-C), 70.9 (d, 2"-C), 120.9 (s, 1 arom. C), 124.1 (d, 1 arom. C), 124.4 (d, 1 arom. C), 125.7 (d, 2 arom. C), 126.1 (d, 1 arom. C), 126.2 (d, 1 arom. C), 126.8 (d, 1 arom. C), 127.6 (d, 1 arom. C), 127.7 (d, 1 arom. C), 127.8 (d, 1 arom. C), 132.4 (s, 1 arom. C), 132.9 (s, 1 arom. C), 134.4 (d, 1 arom. C), 142.5 (s, 1 arom.C), 148.9 (s, 8a-C), 155.4 (s, 2-C), 161.8 (s, 4-C); ms: m/z 316 (M^+, 48), 297 (10), 161 (21), 160 (100), 157 (17), 156 (52), 155 (45), 147 (11), 132 (11), 129 (33), 128 (38), 127 (57), 126 (13), 120 (12), 119 (14), 102 (7), 92 (13), 90 (13), 77 (15), 63 (11), 51 (6), 50 (60).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$ (316.35): C 75.93, H 5.10, N 8.86. Found: C 76.17, H 5.23, N 9.12.

2-(2-Hydroxy-2-(naphthalen-1-yl)ethyl)quinazolin-4(3*H*)-one (**20**).

The compound was obtained as colorless crystals, m.p. 198-200 °C; ^{1}H-NMR: δ 2.00 (dd, 1H, 2'-H_b, J = 9.8, 14.3 Hz), 3.15 (dd, 1H, 2'-H_a, J = 3.2, 14.2 Hz), 5.77 (s, br., OH), 5.96–5.99 (m, 1H, 2'-H), 7.45–7.61 (m, 4H, 6-H, 3 arom. protons), 7.66-7.70 (m, 1H, 8-H), 7.75–7.86 (m, 3H, 7-H, 2 arom. protons), 7.93-7.96 (d, 1H, arom. proton, J = 7.6 Hz), 8.12 (d, 1H, 5-H, J = 7.6 Hz), 8.40 (d, 1H, arom. proton, J = 8.07 Hz), 12.33 (s, 1H, -NH); ^{13}C-NMR: δ 44.1 (t, 1'-C), 68.1 (d, 2"-C), 121.1 (d, 1 arom. C), 123.3 (s, 1 arom. C), 123.6 (d, 1 arom. C), 125.6 (d, 1 arom. C), 125.7 (d, 1 arom. C), 125.8 (d, 2 arom. C), 126.1 (d, 1 arom. C), 127.0 (d, 1 arom. C), 127.8 (d, 1 arom. C), 128.8 (d, 1 arom. C), 130.0 (s, 1 arom. C), 133.4 (s, 1 arom. C), 134.4 (d, 1 arom. C), 140.7 (s, 1 arom.C), 149.0 (s, 8a-C), 155.8 (s, 2-C), 162.0 (s, 4-C); ms: m/z 316 (M^+, 25), 297 (13), 161 (19), 160 (100), 157 (15), 156 (57), 155 (38), 145 (10), 132 (10), 129 (24), 128 (62), 127 (55), 126 (16), 120 (13), 119 (16), 118 (15), 102 (9), 92 (16), 90 (15), 77 (15), 76 (10), 75 (11), 64 (10), 63 (14), 51 (8), 50 (8).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$ (316.35): C 75.93, H 5.10, N 8.86. Found: C 75.71, H 5.14, N 8.40.

General Procedure for the Synthesis of 2-Substituted-4(3*H*)-Quinazolinone Derivatives **21–28**.

To a solution of the corresponding alcohol (**13** – **20**) (0.5 mmol) in methanol (20 ml) trifluoroacetic acid (5 ml) was added and the reaction mixture was stirred under reflux. The reaction was monitored by TLC until completion of the reaction. The reaction mixture was neutralized with aqueous saturated sodium bicarbonate solution and the obtained precipitated solid was collected by filtration and recrystallized from methanol.

(E)-2-(4-Methoxystyryl)quinazolin-4(3*H*)-one (**21**).

The compound was obtained as a pale yellow crystals, m.p. 269-270 °C (lit., [24] 295-298 °C); ^{1}H-NMR ($CDCl_3$/CD_3OD/CF_3COOD): δ 3.82 (s, 3H, CH_3O), 6.86–6.95 (m, 3H, 1'-H, 3"-H, 5"-H), 7.58 (d, 2H, 2"-H, 6"-H, J = 8.8 Hz), 7.65 (t, 1H, 6-H, J = 7.6 Hz), 7.75 (d, 1H, 8-H, J= 8.1 Hz), 7.94 (t, 1H, 7-H, J = 7.3 Hz), 8.09 (d, 1H, CH=CH, J = 15.9 Hz), 8.25 (d, 1H, 5-H, J = 7.3 Hz), ^{13}C-NMR: δ 55.8 (q, (CH_3O), 106.1 (d, C=C), 115.5 (d, 3"-C, 5"-C), 117.3 (s, 4a-C), 119.8 (d, 8-C), 125.4 (s, C=C), 128.1 (d, 5-C), 130.0 (d, 6-C), 132.6 (d, 2"-C, 6"-C), 137.9 (s, 8a-C), 138.7 (d, 7-C), 150.9 (d, 1'-C), 153.9 (s, 4"-C), 160.2 (s, 2-C), 164.9 (s, 4-C); ms: m/z 278 (M^+, 64), 277 (100), 263 (M^+-CH_3, 17), 234 (14), 145 (3), 119 (8), 90 (7), 77 (3).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$ (278.31): C 73.37, H 5.07, N 10.07. Found: C 73.22, H 5.20, N 10.18.

(*E*)-2-(4-(Dimethylamino)styryl)quinazolin-4(3*H*)-one (**22**).

The compound was obtained as yellow crystals, m.p. >260 °C (lit., [24] >300 °C); ^{1}H-NMR ($CDCl_3$/CD_3OD/CF_3COOD): δ 3.02 (s, 6H, CH_3O), 6.56 (d, 1H, CH=CH, J = 16.0 Hz), 6.67 (d, 2H, 2"-H, 6"-H, J = 9.1 Hz), 7.46-7.55 (m, 3H ,6-H, 3"-H, 5"-H), 7.65 (d, 1H, 8-H, J = 8.0 Hz), 7.77-7.84 (m, 1H, 7-H), 8.06 (d, 1H, CH=CH, J = 16.0 Hz), 8.14 (dd, 1H, 5-H, J = 1.3, 8.0 Hz), ^{13}C-NMR: δ 38.9 (q, $N(CH_3)_2$), 103.8 (d, C=C), 111.4 (d, 3"-C, 5"-C), 118.2 (s, 4a-C), 119.2 (d, 8-C), 120.67 (s, 1"-C), 126.6 (d, 5-C), 127.0 (d, 6-C), 131.1 (d, 2"-C, 6"-C), 135.6 (d, 7-C), 139.7 (s, 8a-C), 147.8 (d, C=C), 153.1 (s, 4"-C), 154.1 (s, 2-C), 159.5 (s, 4-C); ms: m/z 291 (M^+, 100), 276 (26), 262 (19), 247 (14), 171 (11), 145 (11), 120 (4), 90 (5), 77 (4).

Anal. Calcd. for $C_{18}H_{17}N_3O$ (291.35): C 74.29, H 5.88, N 14.42. Found: C 74.03, H 5.98, N 14.37.

2-((1*E*,3*E*)-4-(4-(Dimethylamino)phenyl)buta-1,3-dienyl)-quinazolin-4(3*H*)-one (**23**).

The compound was obtained as a orange crystals, m.p. 257 °C; ^{1}H-NMR ($CDCl_3$/CD_3OD/CF_3COOD): δ 2.95 (s, 6H, $N(CH_3)_2$), 6.42 (d, 1H, CH=CH, J = 15.3 Hz), 6.72 (d, 2H, 3"-H, 5"-H, J = 8.3 Hz), 6.92 (dd, 1H, 2'/3'-H, J= 10,8, 15.2 Hz), 7.16

(d, 1H, CH=CH, J = 15.3 Hz), 7.39 (d, 2H, 2''-H, 6''-H, J = 8.8 Hz), 7.48 (ddd, 1H, 6-H, J = 1.0, 7.2, 8.1 Hz), 7.79 (ddd, 1H, 7-H, J = 1.5, 7.2, 8.1 Hz), 7.91 (d, 1H, 8-H, J = 8.1 Hz), 8.04 (dd, 1H, 5-H, J = 1.3, 8.1 Hz), 8.17 (dd, 1H, 2'/3'-H, J = 10.9, 15.3 Hz), ^{13}C-NMR: δ 40.7 (q, $N(CH_3)_2$), 109.8 (d, C=C), 113.2 (d, 3''-C, 5''-C), 118.2 (s, 4a-C), 119.3 (d, 8-C), 122.7 (d, 2'/3'-C), 125.3 (s, 1''-C), 127.0 (d, 5-C), 127.7 (d, 6-C), 130.3 (d, 2''-C, 6''-C), 136.1 (d, 7-C), 138.4 (s, 8a-C), 148.1 (d, C=C), 150.2 (s, 4''-C), 151.1 (d, 2'/3'-C), 153.9 (s, 2-C), 157.4 (s, 4-C); ms: m/z 317 (M^+, 86), 303 (31), 197 (100), 171 (25), 144 (6), 134 (59), 120 (19), 91 (8), 77 (8).

Anal. Calcd. for $C_{20}H_{19}N_3O$ (317.38): C 75.69, H 6.05, N 13.24. Found: C 75.40, H 6.19, N 13.38.

(*E*)-2-(2-(Pyridin-3-yl)vinyl)quinazolin-4(3*H*)-one (**24**).

The compound was obtained as colorless crystals, m.p. 240-241 °C; ^{1}H-NMR ($CDCl_3$/CD_3OD) δ 6.98 (d, 1H, CH=CH, J = 16.4), 7.38–7.47 (m, 2H, 6-H, 3''-H), 7.65–7.78 (m, 2H, 8-H, 7-H), 7.86 (d, 1H, CH=CH, J = 16.4 Hz), 8.00 (dt, 1H, 4''-H, J = 1.7, 8.1 Hz), 8.16–8.20 (m, 1H, 5-H), 8.49 (dd, 1H, 4''-H, J = 1.5, 4.9 Hz), 8.71 (d, 1H, 6''-H, J = 2.2 Hz), ^{13}C-NMR: δ 121.5 (s, 4a-C), 123.5(d, 1 arom. C), 124.9 (d, 1 arom. C), 126.7 (d, 1 arom. C), 127.5 (d, 2 arom. C), 132.0 (s, 5''-C), 135.2 (d, 1 arom. C), 135.5 (d, 1 arom. C), 135.7 (d, 1 arom. C), 149.2 (d, C=C), 149.3 (s, 8a-C), 150.15 (d, C=C), 151.5 (s, 2-H), 163.8 (s, 4-C); ms: m/z 250 (21), 249 (M^+, 88), 248 (100), 222 (10), 221 (29), 220 (37), 205 (5), 196 (13), 168 (6), 129 (6), 120 (15), 119 (17), 110 (7), 104 (9), 92 (12), 90 (14), 77 (10), 76 (10), 64 (7), 63 (8), 51 (10), 50 (7).

Anal. Calcd. for $C_{15}H_{11}N_3O$ (249.27): C 72.28, H 4.45, N 16.86. Found: C 72.30, H 4.50, N 16.72.

(*E*)-2-(2-(Pyridin-4-yl)vinyl)quinazolin-4(3*H*)-one (**25**).

The compound was obtained as colorless crystals, m.p. >260°C; ^{1}H-NMR ($CDCl_3$/CD_3OD) δ 7.11 (d, 1H, CH=CH, J = 16.4 Hz), 7.44–7.54 (m, 3 H, 6-H, 3''-H, 5''-H), 7.68–7.72 (m, 1H, 8-H), 7.72–7.81 (m, 1H, 7-H), 7.81 (d, 1H, CH=CH, J = 16.4), 8.21 (dd, 1H, 5-H, J = 1.5, 7.9 Hz), 8.54–8.57 (m, 2H, 2''-H, 6''-H). ^{13}C-NMR: δ 121.6 (s, 4a-C), 122.5 (d, 2 arom. C), 126.1 (d, 1 arom. C), 126.7 (d, 1 arom. C), 127.6 (d, 1 arom. C), 127.7 (d, 1 arom. C), 135.5 (d, 1 arom. C), 136.4 (d, 1 arom. C), 143.8 (s, 4''-C), 149.1 (s, 8a-C), 150.0 (d, C=C), 151.0 (s, 2-C), 163.6 (s, 4-C); ms: m/z 250 (17), 249 (M^+, 100), 248 (88), 221 (14), 220 (11), 196 (6), 120 (11), 119 (17), 104 (8), 92 (7), 90 (10), 77 (7), 76 (7), 63 (6), 51 (7).

Anal. Calcd. for $C_{15}H_{11}N_3O$ (249.27): C 72.28, H 4.45, N 16.86. Found: C 72.00, H 4.45, N 16.97.

(*E*)-2-(2-(Biphenyl-4-yl)vinyl)quinazolin-4(3*H*)-one (**26**).

The compound was obtained as colorless crystals, m.p. 315-317°C; ^{1}H-NMR ($CDCl_3$/CD_3OD/CF_3COOD): δ 7.14 (d, 1H, CH=CH, J = 16.1), 7.34–7.44 (m, 3H, arom. protons), 7.59–7.83 (m, 8H, arom. protons), 7.90–7.95 (m, 1H, 7-H), 8.24–8.28 (m, 1H, 5-H), 8.30 (d, 1H, CH=CH, J – 16.1 Hz). ^{13}C-NMR: δ 112.3 (d, 1 arom. C), 120.6 (d, 1 arom. C), 122.8 (s, 1 arom. C), 127.7 (d, 2 arom. C), 128.3 (d, 1 arom. C), 128.6 (d, 2 arom. C), 129.2 (d, 1 arom. C), 129.8 (d, 2 arom. C), 129.9 (d, 1 arom. C), 130.6 (d, 2 arom. C), 133.0 (s, 1 arom. C), 137.6 (d, 1 arom. C), 139.4 (s, 1 arom. C), 146.3 (s, 1 arom.C), 149.3 (d, 1 arom. C), 156.0 (s, 8a-C), 160.5 (s, 2-C), 1631.1 (s, 4-C); ms: m/z 325 (30), 324 (M^+, 90), 323 (100), 295 (15), 247 (27), 204 (11), 178 (10), 162 (9), 152 (9), 120 (13), 119 (12), 92 (9), 90 (7), 77 (6).

Anal. Calcd. for $C_{22}H_{16}N_2O$ (324.38): C 81.46, H 4.97, N 8.64. Found: C 81.42, H 4.91, N 8.59.

(*E*)-2-(2-(Naphthalen-2-yl)vinyl)quinazolin-4(3*H*)-one (**27**).

The compound was obtained as colorless crystals, m.p. 273-275 °C; ^{1}H-NMR ($CDCl_3$/CD_3OD/CF_3COOD): δ 7.16 (d, 1H, CH=CH, J = 16.4 Hz), 7.43–7.46 (m, 2H, arom. protons), 7.60 (ddd, 1H, 6-H, J = 1.0, 7.1, 8.1 Hz), 7.72–7.93 (m, 6H, 7-H, 8-H, 4 arom. protons), 8.13 (s, 1H, arom. proton), 8.18 (d, 1H, 5-H, J = 8.1, 1.0 Hz), 8.37 (d, 1H, CH=CH, J = 16.4 Hz). ^{13}C-NMR: δ 111.1 (d, 1 arom. C), 118.8 (s, 1 arom. C), 119.2 (d, 1 arom. C), 122.5 (d, 1 arom. C), 126.9 (d, 1 arom. C), 127.2 (d, 1 arom. C), 127.5 (d, 1 arom. C), 128.4 (d, 1 arom. C), 128.7 (d, 1 arom. C), 128.9 (d, 1 arom. C), 129.1 (d, 1 arom. C), 130.5 (s, 1 arom. C), 132.7 (d, 1 arom. C), 133.0 (s, 1 arom. C), 135.1 (s, 1 arom. C), 136.6 (d, 1 arom. C), 137.8 (s, 1 arom. C), 149.0 (d, 1 arom. C), 155.0 (s, 2-C), 159.3 (s, 4-C); ms: m/z 299 (13), 298 (68), 297 (M^+, 100), 269 (12), 178 (4), 149 (5), 152 (11), 151 (6), 149 (5), 120 (8), 119 (6), 92 (5), 90 (4).

Anal. Calcd. for $C_{20}H_{14}N_2O$ (298.34): C 80.52, H 4.73, N 9.39. Found: C 80.36, H 4.51, N 9.19.

(*E*)-2-(2-(Naphthalen-1-yl)vinyl)quinazolin-4(3*H*)-one (**28**).

The compound was obtained as colorless crystals, m.p. >260 °C; ^{1}H-NMR ($CDCl_3$/CD_3OD/CF_3COOD): δ 7.25 (d, 1H, CH=CH, J = 16.2 Hz), 7.54–7.75 (m, 4H, 6-H, 8-H, 2arom. protons), 7.80–7.90 (m, 2H, arom. protons), 7.95–8.09 (m, 3H, 7-H, 2arom. protons), 8.31 (d, 1H, 5-H, J = 8.1, 1.2 Hz), 8.40 (d, 1H, arom. proton, J = 8.4 Hz), 9.21 (d, 1H, CH=CH, J = 16.2 Hz). ^{13}C-NMR: δ 114.0 (d, 1 arom. C), 120.2 (d, 1 arom. C), 123.3 (s, 1 arom. C), 123.5 (d, 1 arom. C), 126.3 (d, 1 arom. C), 127.1 (d, 1 arom. C), 127.5 (d, 1 arom. C), 128.3 (d, 1 arom. C), 128.6 (d, 1 arom. C), 129.8 (d, 1 arom. C), 129.9 (s, 1 arom. C), 132.6 (s, 1 arom. C), 134.0 (s, 1 arom. C), 134.2 (s, 1 arom. C), 134.7 (d, 1 arom. C), 137.7 (d, 1 arom. C), 146.3 (s, 1 arom. C), 146.4 (d, 1 arom. C), 146.6 (d, 1 arom. C), 155.8 (s, 4-C); ms: m/z 299 (15), 298 (73), 297 (M^+, 100), 269 (7), 178 (6), 152 (18), 151 (10), 120 (9), 119 (7), 92 (6), 90 (4).

Anal. Calcd. for $C_{20}H_{14}N_2O$ (298.34): C 80.52, H 4.73, N 9.39. Found: C 80.25, H 4.82, N 9.14.

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