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Antitumor agents 287. Substituted 4-amino-2*H*-pyran-2-one (APO) analogs reveal a new scaffold from neo-tanshinlactone with in vitro anticancer activity

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ABSTRACT

4-Amino-2*H*-benzo[*h*]chromen-2-one (ABO) and 4-amino-7,8,9,10-tetrahydro-2*H*-benzo[*h*]chromen-2-one (ATBO) analogs were found to be significant in vitro anticancer agents in our previous research. Our continuing study has now discovered a new simplified (monocyclic rather than tricyclic) class of cytotoxic agents, 4-amino-2*H*-pyran-2-one (APO) analogs. By incorporating various substituents on the pyranone ring, we have established preliminary structure–activity relationships (SAR). Analogs **19**, **20**, **23**, and **26**–**30** displayed significant tumor cell growth inhibitory activity in vitro. The most active compound **27** exhibited ED_{50} values of 0.059–0.090 μM.

In 2004, our group first isolated and synthesized neo-tanshinlactone (**1**).[1] Compound **1** was 10-fold more potent and 20-fold more selective as compared with tamoxifen citrate against the ER+ human breast cancer cell lines MCF-7 and ZR-75-1. Further structural optimization led to its 4-ethyl analog **2**, which displayed significant and selective anti-breast cancer activity both in vitro and in vivo.[2,3] Moreover, **2** was selective for a subset of breast cancer-derived cell lines and significantly less active against normal breast-derived tissue. In order to explore the effect of individual rings on the anticancer activity, identify new lead compounds, and discover new chemical entities, we designed and reported five classes of new anticancer agents, including 2-(furan-2-yl) naphthalen-1-ol (FNO),[4] 6-phenyl-4*H*-furo[3,2-*c*]pyran-4-one (AFPO),[5] tetrahydronaphthalene-1-ol (TNO),[6] 4-amino-2*H*-benzo[*h*]chromen-2-one (ABO, **3**, Fig. 1),[7] and 4-amino-7,8,9,10-tetrahydro-2*H*-benzo[*h*]chromen-2-one (ATBO, **4**, Fig. 1)[8] analogs. Interestingly, the neo-tanshinlactone-inspired synthesis of a breast cancer selective ABO series was reported independently by others.[9]

Importantly, ABO and ATBO compounds displayed much higher potency than **1**-analogs, which encouraged us to further investigate these scaffolds. Structure–activity relationship (SAR) studies on **3** and **4** indicated that (1) a secondary amine (R^2 or R^3 = H) is preferred over tertiary amine (R^2 and $R^3 \neq$ H), (2) bulky groups are favored at the R^2/R^3 position, (3) a 3′-bromophenyl group can cause a dramatic loss of potency, and (4) a non-aromatic ring-A can increase potency and cancer cell line selectivity for certain

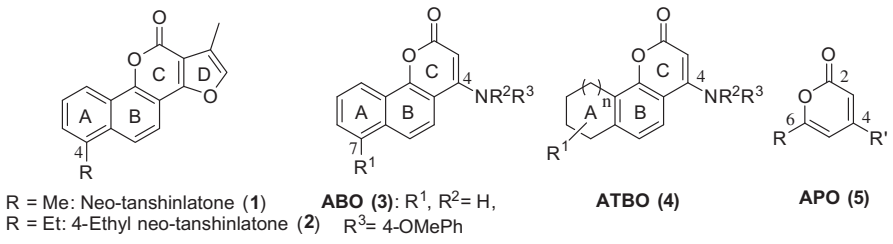

Figure 1. Structures of neo-tanshinlactone (**1**), 4-ethyl neo-tanshinlactone (**2**), previously reported ABO (**3**) and ATBO (**4**) scaffolds, and newly designed APO scaffold (**5**).

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Table 1
Cytotoxicity of **12**–**30** against human tumor cell line panel

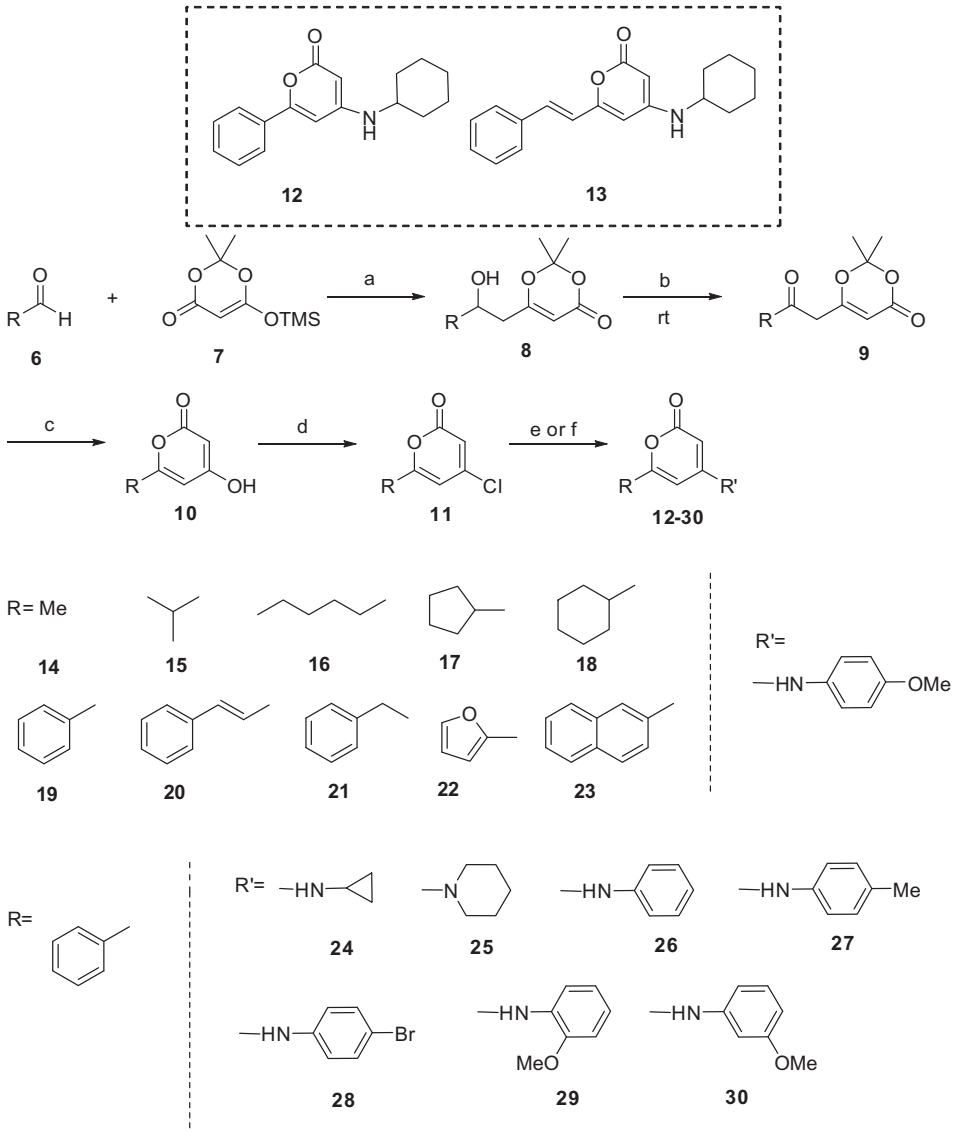
Compd	ED_{50}[a] (μM)				
	KB	KB-VIN	A549	DU145	SKBR-3
3	0.11	0.13	0.17	0.11	0.13
12	9.69	9.15	16.02	7.47	10.91
13	1.25	1.24	2.02	1.23	1.53
14	>30	>30	>30	>30	>30
15	>30	>30	>30	>30	>30
16	4.42	4.84	10.06	5.94	4.93
17	5.42	4.98	8.38	5.42	4.73
18	4.62	4.39	8.32	8.61	5.29
19	0.093	0.098	0.16	0.12	0.079
20	0.11	0.10	0.15	0.11	0.083
21	1.62	1.30	2.42	1.60	1.34
22	1.91	1.46	2.66	1.95	1.76
23	0.15	0.13	0.18	0.15	0.13
24	>30	>30	>30	>30	>30
25	>30	>30	>30	>30	>30
26	0.12	0.15	0.13	0.098	0.13
27	0.067	0.059	0.064	0.073	0.090
28	0.31	0.24	0.32	0.34	0.40
29	0.44	0.49	0.35	0.37	0.54
30	0.63	0.55	0.49	0.66	0.74

[a] Mean from three or more independent tests.

analogs. Our studies also indicated that the lactone ring-C is critical to the cytotoxic activity.[3,7,8] Therefore, we designed a structurally simplified monocyclic scaffold (**5**, Fig. 1) and incorporated various substituents at the R and R′ positions to explore the contributions of ring-A and -B, develop new chemical entities and new leads, and establish the SAR. Herein, we report the design, synthesis, and biological activity of 4-amino-2*H*-pyran-2-one (APO) analogs.

As a first step in the current work, we designed two model compounds **12** and **13** by eliminating the fused ring-A/B system and incorporating pendant phenyl and styryl groups, respectively, on the remaining pyranone C-ring. 6-Substituted 4-hydroxy-2*H*-pyran-2-one **10** was synthesized according to the method reported by Bach and Kirsch.[10] The appropriate aldehyde (**6**) and an acetoacetate equivalent (**7**) underwent a vinylogous Mukaiyama aldol addition to give **8**, which was oxidized to **9** using the Dess–Martin method. A thermal cyclization of **9** yielded 4-hydroxy-2*H*-pyranone **10**. Chlorination followed by amination of **10** provided model compounds **12** and **13**.[7,11]

Analogs **12** and **13** were tested for in vitro cytotoxic activity against a panel of human tumor cell lines according to previously published methods (Table 1).[3] Cell lines included A549 (non-small cell lung cancer), DU145 (prostate cancer cell line),



Scheme 1. Reagents and conditions: (a) $TiCl_4$, CH_2Cl_2, −78 °C; (b) Dess–Martin reagent, rt; (c) toluene, reflux; (d) $POCl_3$, Et_3N, reflux, 1 h; (e) aliphatic amines, EtOH, reflux, 2 h; (f) aromatic amines, ethylene glycol, 160 °C, 1 h.

KB (nasopharyngeal carcinoma), and KB-VIN (vincristine-resistant MDR KB subline), SK-BR-3 (estrogen receptor negative, HER2 over-expressing breast cancer). Importantly, **13** showed significant inhibition of all human cancer cell lines tested with ED_{50} values from 1.23 to 2.02 μM, while **12** displayed moderate activity.

Encouraged by these promising results, analogs **14**–**30** were designed to establish SAR correlations as well as to optimize structure and identify more active derivatives with the desired biological properties[11]. Firstly, we installed various groups at the pyranone 6-position (R group) to explore the effect of group size, ring size, and aromaticity. Secondly, different substituents at the pyranone 4-position (R′ group) were investigated while retaining the best R group. As shown in Scheme 1, new analogs **14**–**30** were obtained through the five-step procedure similarly to **12** and **13**, and then evaluated against five human tumor cell lines from different tissues.

Compounds **14** and **15** with methyl and isopropyl R groups were not active, and **16**–**18** with pentyl, cyclopentyl, and cyclohexyl groups showed moderate activity. These results suggested that long alkyl chains and cyclic alkyl groups were favored at the pyranone 6-position. Compounds **19**–**23**, which contain different aromatic R groups, including phenyl, styryl, benzyl, furanyl, and naphthyl, displayed significant activity. Especially, **19** and **20** with phenyl and styryl groups, respectively, were the most potent analogs with ED_{50} values of 0.079–0.163 μM, and were equally or slightly more potent than ABO analog **3**. The results indicated that an aromatic ring at the pyranone 6-position may be critical to the cytotoxic activity.

Based on structural simplicity and chemical availability as well as the above results, we designed analogs **24**–**30**, which have various substituents at the pyranone 4-position and a phenyl group fixed at the 6-position. Among them, **26**–**30** with substituted aniline groups displayed significant activity against all tested tumor cell lines compared with analogs containing cycloalkyl groups, including cyclohexylamine (**12**), cyclopropylamine (**24**), and piperidine (**25**). The latter two compounds totally lost cytotoxic activity. These data indicate that an aromatic amino R′ group is favored at the 4-position. In addition, the position and type of substituent on the aniline ring played an important role in the cytotoxic activity. The rank order of potency for all aromatic analogs against KB was **27** (4′-Me) > **19** (4′-OMe) > **26** (H) > **28** (4′-Br) ∼ **29** (2′-OMe) ∼ **30** (3′-OMe). 4-Methylaniline-substituted **27** was the most potent analog with ED_{50} values of 0.059–0.090 μM. It was about twofold more potent than ABO analog **3**.

Overall, **19** and **27** showed greater in vitro antitumor activity than other analogs, suggesting that the combination of a phenyl group at the 6-position and a 4′-methyl- or 4′-methoxy-aniline at the 4-position is favored for the APO analogs.

In summary, we designed and developed a new class (APO) of in vitro anticancer agents, through structural simplification and optimization. Lead compounds displayed potent antitumor activity with ED_{50} values in the low micromolar range. SAR studies indicated that: (1) an aromatic ring such as phenyl and styryl at the pyranone 6-position is critical to the antitumor activity, (2) a secondary amine at the 4-position is preferred over a tertiary amine, (3) aromatic amine groups at the 4-position are crucial, and (4) substituents on the aromatic amine group can increase potency. Compounds **19** and **27** were the most potent analogs (ED_{50} values of 0.059–0.163 μM) among all derivatives, and thus, are new lead compounds that are promising for further development of potential clinical trials candidates.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.02.084.

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11. **Spectroscopic data**: *4-(Cyclohexylamino)-6-phenyl-2H-pyran-2-one* (**12**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (m, 2H, Ar-*H*), 7.39 (m, 3H, Ar-*H*), 6.21 (d, 1H, *J* = 2.0 Hz,), 5.11 (d, 1H, *J* = 1.6 Hz, 3-*H*), 4.94 (d, 1H, *J* = 7.2 Hz, N*H*), 3.29 (m, 1H, NC*H*), 2.05 (m, 2H, NCHCH_2), 1.78 (m, 2H, NCHCH_2), 1.26 (m, 6H, cyclohexyl-*H*). MS *m/z* 270 (M^++1). *(E)-4-(Cyclohexylamino)-6-styryl-2H-pyran-2-one* (**13**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.47 (m, 3H, Ar & olefin-*H*), 7.32 (m, 3H, Ar-*H*), 6.53 (d, 1H, *J* = 13.6 Hz, olefin-*H*), 5.71 (s, 1H, 3-*H*), 5.08 (d, 1H, *J* = 1.6 Hz,), 4.73 (d, 1H, *J* = 7.2 Hz, N*H*), 3.27 (m, 1H, NC*H*), 2.05 (m, 2H, NCHCH_2), 1.78 (m, 2H, NCHCH_2), 1.26 (m, 6H, cyclohexyl-*H*). MS *m/z* 296 (M^++1). *4-[(4-Methoxyphenyl)amino]-6-methyl-2H-pyran-2-one* (**14**): ^{1}H NMR (400 MHz, CD_3OD): δ 7.14 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 6.97 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 5.97 (d, 1H, *J* = 2.0 Hz, 5-*H*), 5.14 (d, 1H, *J* = 1.6 Hz, 3-*H*), 3.82 (s, 1H, 4′-OCH_3), 2.20 (d, 3H, *J* = 0.8 Hz, 6-CH_3). MS *m/z* 230 (M^+−1). *6-Isopropyl-4-[(4-methoxyphenyl)amino]-2H-pyran-2-one* (**15**): ^{1}H NMR (400 MHz, CD_3OD): δ 7.15 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 6.97 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 5.97 (d, 1H, *J* = 2.0 Hz, 5-*H*), 5.15 (d, 1H, *J* = 1.6 Hz, 3-*H*), 3.81 (d, 3H, *J* = 1.2 Hz, 4′-OCH_3), 2.72 (h, 1H, *J* = 6.8 Hz, isopropyl-*H*), 1.24 (d, 6H, *J* = 6.8 Hz, isopropyl-*H*). MS *m/z* 258 (M^+−1). *4-[(4-Methoxyphenyl)amino]-6-pentyl-2H-pyran-2-one* (**16**): ^{1}H NMR (400 MHz, CD_3OD): δ 7.15 (d, 2H, *J* = 9.2 Hz, Ar-*H*), 6.97 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 5.97 (d, 1H, *J* = 2.4 Hz, 5-*H*), 5.15 (d, 1H, *J* = 2.4 Hz, 3-*H*), 3.81 (s, 3H, 4′-OCH_3), 2.46 (t, 2H, *J* = 7.6 Hz, pentyl-*H*), 1.66 (p, 2H, *J* = 7.6 Hz, pentyl-*H*), 1.34–1.38 (m, 4H, pentyl-*H*), 0.93 (t, 3H, *J* = 7.2 Hz, pentyl-*H*). MS *m/z* 286 (M^+−1). *6-Cyclopentyl-4-[(4-methoxyphenyl)amino]-2H-pyran-2-one* (**17**): ^{1}H NMR (400 MHz, CD_3OD): δ 7.14 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 6.97 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 5.99 (d, 1H, *J* = 2.4 Hz, 5-*H*), 5.14 (d, 1H, *J* = 2.0 Hz, 3-*H*), 3.81 (s, 3H, 4′-OCH_3), 2.40 (m, 1H, cyclopentyl-*H*), 2.89 (p, 1H, *J* = 8.0 Hz, cyclopentyl-*H*), 1.96–2.01 (m, 2H, cyclopentyl-*H*), 1.66–1.82 (m, 6H, cyclopentyl-*H*). MS *m/z* 284 (M^+−1). *6-Cyclohexyl-4-[(4-methoxyphenyl)amino]-2H-pyran-2-one* (**18**): ^{1}H NMR (400 MHz, CD_3OD): δ 7.14 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 6.97 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 5.95 (s, 1H, 5-*H*), 5.15 (s, 1H, 3-*H*), 3.81 (s, 1H, 4′-OCH_3), 2.40 (m, 1H, cyclohexyl-*H*), 1.72–1.94 (m, 5H, cyclohexyl-*H*), 1.25–1.47 (m, 5H, cyclohexyl-*H*). MS *m/z* 298 (M^+−1). *4-[(4-Methoxyphenyl)amino]-6-phenyl-2H-pyran-2-one* (**19**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.85 m, 2H, Ar-*H*, 7.48–7.51 m, 3H, Ar-*H*, 7.20 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.00 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 6.66 (d, 1H, *J* = 2.0 Hz,5-*H*), 5.29 (d, 1H, *J* = 2.0 Hz, 3-*H*), 3.83 (s, 3H, 4′-OCH_3). MS *m/z* 292 (M^+−1). *(E)-4-[(4-Methoxyphenyl)amino]-6-styryl-2H-pyran-2-one* (**20**): ^{1}H NMR (400 MHz, CD_3OD): δ 7.60 d, 2H, *J* = 7.2 Hz, Ar-H, 7.33−7.44 m, 4H, Ar & olefin-*H*, 7.17–7.20 (m, 2H, Ar-*H*), 6.98–7.00 (m, 2H, Ar-*H*), 6.85 (d, 1H, *J* = 16.0 Hz, olefin-*H*), 6.20 (d, 1H, *J* = 2.0 Hz, 5-*H*), 5.25 (d, 1H, *J* = 1.6 Hz, 3-*H*), 3.82 (s, 1H, 4′-OCH_3). MS *m/z* 318 (M^+−1). *6-Benzyl-4-[(4-methoxyphenyl)-amino]-2H-pyran-2-one* (**21**): ^{1}H NMR (400 MHz, CD_3OD): δ 7.30–7.36 m, 5H, Ar-*H*, 7.11 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 6.95 (d, 2H, *J* = 9.2 Hz, Ar-*H*), 5.89 (s, 1H, 5-*H*), 5.14 (d, 1H, *J* = 1.6 Hz, 3-*H*), 3.80 (s, 3H, 4′-OCH_3), 3.79 (s, 2H, 6-CH_2). MS *m/z* 306 (M^+−1). *6-(Furan-2-yl)-4-[(4-methoxyphenyl)amino]-2H-pyran-2-one* (**22**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 s, 1H, Ar-*H*), 7.18 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 6.98–7.00 (m, 3H, Ar-*H*), 6.61–6.63 (m, 1H, Ar-*H*), 6.49 (d, 1H, *J* = 1.6 Hz, 5-*H*), 5.22 (d, 1H, *J* = 2.0 Hz, 3-*H*), 3.82 (s, 3H, 4′-OCH_3). MS *m/z* 282 (M^+−1). *4-[(4-Methoxyphenyl)amino]-6-(naphthalen-2-yl)-2H-pyran-2-one* (**23**): ^{1}H NMR (400 MHz, CD_3OD): δ 8.42 s, 1H, Ar-*H*, 7.86–7.99 m, 4H, Ar-*H*, 7.57–5.59 m, 2H, Ar-*H*, 7.23 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.02 (d, 2H, *J* = 9.2 Hz, Ar-*H*), 6.81 (d, 1H, *J* = 2.0 Hz,5-*H*), 5.33 (d, 1H, *J* = 2.0 Hz, 3-*H*), 3.84 (s, 3H, 4′-OCH_3). MS *m/z* 342 (M^+−1). *4-(Cyclopropylamino)-6-phenyl-2H-pyran-2-one* (**24**): ^{1}H NMR (400 MHz, CD_3OD): δ 7.80 m, 2H, Ar-*H*, 7.46 m, 3H, Ar-*H*, 6.46 (s, 1H, 5-*H*), 5.41 (s, 1H, 3-*H*), 2.52 (s, 1H, 1′-*H*), 0.85 (d, 2H, *J* = 6.4 Hz, 2′ & 3′-*H*), 0.58 (m, 2H, 2′ & 3′-*H*). MS *m/z* 226 (M^+−1). *6-Phenyl-4-(piperidin-1-yl)-2H-pyran-2-one*

(**25**) ^{1}H NMR (400 MHz, CD_3OD): δ 7.89–7.92 m, 2H, Ar-*H*, 7.47–7.49 m, 3H, Ar-*H*, 6.92 (d, 1H, *J* = 1.6 Hz, 5-*H*), 5.28 (d, 1H, *J* = 2.0 Hz, 3-*H*), 3.57 (t, 4H, *J* = 4.8 Hz, 2′ & 6′-*H*), 1.68–1.75 (m, 6H, 3′, 4′, & 5′-*H*). MS *m*/*z* (M^+-1). *6-Phenyl-4-(phenylamino)-2H-pyran-2-one* (**26**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.42 s, 1H, N*H*), 7.76–7.78 m, 2H, Ar-*H*, 7.53–7.56 m, 3H, Ar-*H*, 7.44 (t, 2H, *J* = 7.6 Hz, Ar-*H*), 7.28 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 7.21 (t, 1H, *J* = 7.2 Hz, Ar-*H*), 6.70 (d, 1H, *J* = 1.6 Hz, 5-*H*), 5.34 (t, 1H, *J* = 1.2 Hz, 3-*H*). MS *m*/*z* 262 (M^+-1). *6-Phenyl-4-(p-tolylamino)-2H-pyran-2-one* (**27**): ^{1}H NMR (400 MHz, CD_3OD): δ 7.83–7.86 m, 2H, Ar-*H*, 7.50–7.52 m, 3H, Ar-*H*, 7.26 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 7.17 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 6.69 (d, 1H, *J* = 2.0 Hz, 5-*H*), 5.41 (d, 1H, *J* = 2.0 Hz, 3-*H*), 2.37 (s, 3H, C*H*$_3$). MS *m*/*z* 276 (M^+-1). *4-[(4-Bromophenyl)amino]-6-phenyl-2H-pyran-2-one* (**28**): ^{1}H NMR (400 MHz, CD_3OD): δ 7.84–7.87 m, 2H, Ar-*H*, 7.59 (d, 1H, *J* = 8.4 Hz, Ar-*H*), 7.50–7.52 m, 3H, Ar-*H*, 7.23 (d, 1H, *J* = 8.8 Hz, Ar-*H*), 6.70 (d, 1H, *J* = 2.0 Hz, 5-*H*), 5.50 (d, 1H, *J* = 2.0 Hz, 3-*H*). MS *m*/*z* 340 (M^+-1). *4-[(2-Methoxyphenyl)amino]-6-phenyl-2H-pyran-2-one* (**29**): ^{1}H NMR (400 MHz, CD_3OD): δ 7.83–7.86 m, 2H, Ar-*H*, 7.50–7.52 m, 3H, Ar-*H*, 7.34 (t, 1H, *J* = 8.0 Hz, Ar-*H*), 6.81–6.89 (m, 3H, Ar-*H*), 6.71 (d, 1H, *J* = 2.0 Hz, 5-*H*), 5.53 (d, 1H, *J* = 2.0 Hz, 3-*H*), 3.82 (s, 3H, 4′-OC*H*$_3$). MS *m*/*z* 292 (M^+-1). *4-[(3-Methoxyphenyl)amino]-6-phenyl-2H-pyran-2-one* (**30**): ^{1}H NMR (400 MHz, CD_3OD): δ 7.83–7.86 m, 2H, Ar-*H*, 7.50–7.52 m, 3H, Ar-*H*, 7.34 (t, 1H, *J* = 8.0 Hz, Ar-*H*), 6.81–6.89 (m, 3H, Ar-*H*), 6.71 (d, 1H, *J* = 2.0 Hz,5-*H*), 5.53 (d, 1H, *J* = 2.0 Hz, 3-*H*), 3.82 (s, 3H, 4′-OC*H*$_3$). MS *m*/*z* 292 (M^+-1).