

Supplementary information to

**AROMATASE INHIBITORY ACTIVITY OF
1,4-NAPHTHOQUINONE DERIVATIVES AND QSAR STUDY**

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<http://dx.doi.org/10.17179/excli2017-309>

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**STRUCTURE-ACTIVITY RELATIONSHIPS OF THE COMPOUNDS 1–11:
A DETAILED DISCUSSION**

Structure-activity relationships (SAR) of the compounds **1–11** revealed that the chloro (Cl) group at C-2 position of compound **1** was replaced by amino group to give 2-substituted amino-3-chloro compounds (**2–11**) with lower to inactive aromatase inhibitory activities, except for compound **4** which still exhibited equipotent activity as compared to compound **1**. The 2-substituted amino groups were *N*-phenyl and *N*-alkyl of secondary amines, but compound **4** was tertiary amine. Moreover, the phenyl groups of 2-amino position constitute electron donating and electron withdrawing substituents (R) at *ortho*-, *meta*-, and *para*-positions. Obviously, the enhanced activity of inactive compound (**3**) was noted when R = electron donating (*N*-phenyl or aniliny) to give compound **8** (IC₅₀ = 1.9 μM) comparing to R = electron withdrawing groups (COCH₃ and COOH). It was found that *meta*-COCH₃ (**6**, IC₅₀ = 3.1 μM) exhibited stronger activity than *para*-COCH₃ (**7**, IC₅₀ = 5.3 μM) and *ortho*-COOH (**5**, IC₅₀ = 18.0 μM).

In case of *N*-alkyl substituted compound (**2**, R = C₄H₉) and *N*-alkylaryl (**10**, R = CH₂CH₂Ph), the latter (**10**) displayed better activity than the former (**2**). When dimethoxy (diOMe) groups were introduced to the phenyl (Ph) ring of compound **10**, compound **11** was obtained with totally loss of activity. It could be presumably suggested that diOCH₃ groups made the molecule (**11**) arrange in an inappropriate form in interacting with the target enzyme.

Interestingly, introducing methyl (CH₃) group to the secondary amine of inactive compound **3** resulted in the most potent tertiary amine compound (**4**). This could be possibly due to the lipophilicity and electron rich moiety of the amine **4**, which are required for the most potent activity comparing to the other secondary amines. Similarly, the most potent activity of compound **1** could be attributed to the electronic and lipophilic properties of the Cl group in enhancing the activity. In addition to *N*-phenyl moieties at position 2, *N*-quinolinyl compound **9** exhibited relatively high inhibitory activity (IC₅₀ = 4.7 μM). Again, this could be possibly due to the hydrophobic effect of the condensed quinolinyl ring.

Table S1: Values of informative molecular descriptors of tested compounds (**1-11**) and virtually modified compounds (series **1-11**)

Compound	Mor04m	Mor08e	H8m	G1v	SIC2
1	1.226	-0.928	0.000	0.193	0.707
2	1.839	0.249	0.010	0.167	0.808
3	1.672	-0.494	0.001	0.169	0.673
4	1.104	-0.728	0.002	0.190	0.682
5	2.245	-0.182	0.053	0.165	0.755
6	1.885	-0.642	0.004	0.163	0.765
7	2.320	-0.280	0.005	0.179	0.751
8	1.499	-0.478	0.021	0.169	0.612
9	2.373	-1.001	0.039	0.179	0.770
10	1.799	-0.071	0.010	0.191	0.720
11	1.151	0.295	0.032	0.155	0.779
1a	0.479	-0.644	0.000	0.193	0.707
1b	-5.734	-0.583	0.000	0.193	0.707
1c	0.465	-0.757	0.000	0.193	0.707
2a	1.625	0.246	0.000	0.171	0.824
2b	1.664	-0.027	0.000	0.175	0.814
2c	1.322	0.839	0.013	0.163	0.802
2d	1.260	0.666	0.001	0.167	0.816
2e	1.315	0.560	0.000	0.171	0.805
2f	1.264	-0.132	0.000	0.175	0.726
3a	2.165	-1.458	0.024	0.177	0.675
3b	1.687	0.111	0.008	0.162	0.699
4a	0.692	-0.911	0.002	0.162	0.705
4b	0.845	-0.745	0.005	0.159	0.724
4c	1.743	-0.134	0.012	0.159	0.705

Table S1 (cont.): Values of informative molecular descriptors of tested compounds (1-11) and virtually modified compounds (series 1-11)

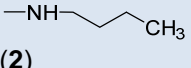
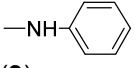
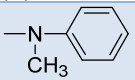
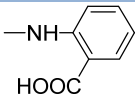
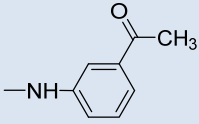
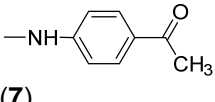
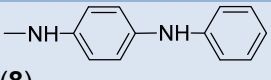
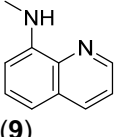
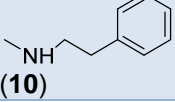
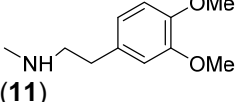
Compound	Mor04m	Mor08e	H8m	G1v	SIC2
4d	0.753	0.100	0.019	0.169	0.723
4e	1.513	-1.588	0.030	0.163	0.683
4f	0.585	-1.436	0.071	0.151	0.700
5a	2.035	-0.693	0.003	0.165	0.775
5b	2.349	-0.444	0.002	0.165	0.760
5c	1.455	-1.125	0.088	0.162	0.773
5d	1.622	-0.686	0.005	0.162	0.760
6a	2.852	-0.960	0.018	0.163	0.765
6b	1.980	-1.536	0.106	0.160	0.764
6c	1.441	-0.938	0.039	0.174	0.764
7a	2.837	-1.022	0.003	0.193	0.751
7b	1.834	-1.161	0.007	0.160	0.752
7c	1.448	-0.472	0.007	0.174	0.752
8a	0.732	-0.473	0.012	0.186	0.644
8b	1.864	-0.558	0.002	0.156	0.627
8c	0.612	-0.835	0.037	0.165	0.659
9a	1.587	-0.726	0.025	0.163	0.781
9b	2.209	-0.575	0.024	0.179	0.763
9c	2.190	-0.814	0.032	0.179	0.752
10a	2.067	-0.591	0.031	0.165	0.699
10b	1.383	0.718	0.067	0.159	0.724
10c	1.361	-0.395	0.046	0.162	0.705
11a	0.575	0.629	0.091	0.153	0.778
11b	1.783	-0.222	0.035	0.166	0.776
11c	0.665	0.326	0.111	0.173	0.775

Table S2: Experimental and predicted aromatase inhibitory activities (pIC₅₀) of compounds 1-11

Compound	Experimental activity	Predicted activity	Residual
1	0.301	0.348	0.047
2	-0.940	-1.013	-0.073
3	- ^a	- ^a	- ^a
4	0.301	0.249	-0.052
5	-1.255	-1.205	0.050
6	-0.491	-0.420	0.071
7	-0.724	-0.763	-0.039
8	-0.279	-0.324	-0.045
9	-0.672	-0.737	-0.065
10	-0.519	-0.467	0.052
11	- ^a	- ^a	- ^a

^aThe compound was experimentally inactive and was excluded from the data set of QSAR analysis.

Table S3: Effects of substituents on 2-amino-3-chloro-1,4-naphthoquinone core structure on important descriptor values and aromatase inhibitory activity

Panel	Substituent at position 2 (compound)	Modification effect ^a	Altered descriptors
1	 (2)	↓ activity: 2 < 1	↑: Mor04m, Mor08e ↓: G1v
2	 (3)	↓ activity: 3 (IA) < 1 (IA)	↑: Mor04m, Mor08e ↓: G1v
3	 (4)	-CH ₃ : ↑ activity : 4 > 3	↑: G1v ↓: Mor04m, Mor08e
4	 (5)	-COOH : ↓ activity : 5 < 4	↑: Mor04m, Mor08e, H8m ↓: G1v
5	 (6)	<i>m</i> -COCH ₃ : ↓ activity : 6 < 4	↑: Mor04m, Mor08e, H8m ↓: G1v
6	 (7)	<i>p</i> -COCH ₃ : ↓ activity: 7 < 4	↑: Mor04m, Mor08e, H8m ↓: G1v
7	 (8)	-C ₆ H ₆ N: ↓ activity : 8 < 4	↑: Mor04m, Mor08e, H8m ↓: G1v
8	 (9)	Quinolinyl : ↑ activity : 9 > 2, 9 > 3	↑: Mor04m, H8m, G1v ↓: Mor08e
9	 (10)	Phenyl ring: ↑ activity : 10 > 2	↑: G1v ↓: Mor04m, Mor08e
10	 (11)	-OMe : ↓ activity : 11 (IA) < 10 (A)	↑: Mor08e ↓: Mor04m, G1v

IA = inactive, A = active. ^a Experimental activity of the tested compounds was used for comparison. The deteriorate effects were found in all tested compounds when compared to the prototype 1, except for compound 4.

Table S4: Predicted aromatase inhibitory activity (pIC₅₀) of virtually modified compounds (series 1-11) and experimental aromatase inhibitory activity of reference drugs

Compound	pIC ₅₀	Compound	pIC ₅₀
1a	0.550 ^a	6a	-0.898 ^b
1b	3.582 ^a	6b	-0.898 ^b
1c	0.614 ^a	6c	-0.294 ^b
2a	-0.758 ^b	7a	-0.494 ^b
2b	-0.599 ^b	7b	-0.217 ^b
2c	-1.047 ^c	7c	-0.265 ^b
2d	-0.819 ^b	8a	0.259 ^a
2e	-0.742 ^b	8b	-0.390 ^b
2f	-0.253 ^b	8c	0.124 ^a
3a	-0.151 ^b	9a	-0.465 ^b
3b	-0.718 ^b	9b	-0.696 ^b
4a	0.326 ^a	9c	-0.618 ^b
4b	0.099 ^a	10a	-0.712 ^b
4c	-0.684 ^b	10b	-1.391 ^c
4d	-0.311 ^b	10c	-0.611 ^b
4e	0.071 ^a	11a	-1.243 ^c
4f	0.016 ^a	11b	-0.865 ^b
5a	-0.506 ^b	11c	-1.136 ^c
5b	-0.762 ^b	Ketoconazole	-0.415 ^d
5c	-0.698 ^b	Letrozole	3.482 ^d
5d	-0.329 ^b		

^a Highly active compound

^b Moderately active compound

^c Weakly active to inactive compound

^d Experimental activity

Table S5: Summary of structurally modified compounds (series 1-11)

Series	Comparison	Affected de-descriptors	Related properties	Notes
1	Disubstitution at C-2 and C-3 position: ↑activity di-I > di-F > di-Br > di-Cl (1b > 1c > 1a > 1)	Mor04m ^a Mor08e	Mass Electronegativity	1b ^b is the most potent of the series 1. All modifications ↑activity. Disubstitution with high EN atoms can markedly improve activity. All compounds in series 1 had the same values of H8m = 0, G1v = 0.193 and SIC2 = 0.707
2	Length of substituted alkyl chain on amino group: short chain > long chain (2f > 2b > 2e > 2a > 2d > 2 > 2c)	Mor08e ^a Mor04m G1v	Electronegativity Mass <i>van der Waals</i> volume	2f ^b is the most potent of the series 2. All modifications ↑activity, except 2c . Dimethyl substitution (2f) provide the best activity than long alkyl chain.
	CH ₃ substitution on NH group: ↓activity (2b > 2e , 2a > 2d , 2 > 2c)	Mor08e ^c	Electronegativity	Within the same length of alkyl chain, the ones with additional CH ₃ substitution on amino group are less potent.
3	Type of substituted ring on NH group: 1-adamantyl > cyclohexyl > phenyl (3a > 3b > 3)	Mor04m Mor08e ^c G1v	Mass Electronegativity <i>van der Waals</i> volume	3a ^b is the most potent of the series 3. All modifications ↑activity. Substitution with 1-adamantyl group provides the best activity.
4	Within the same length of substituted alkyl chain on N atom: phenyl > 1-adamantyl > cyclohexyl (4a > 4f > 4d)	Mor04m Mor08e ^c G1v	Mass Electronegativity <i>van der Waals</i> volume	4a ^b is the most potent of the series 4. All modifications ↓activity, except 4a . Phenyl derivative substituted with 2C alkyl chain provided the most potent activity.
	Length of substituted alkyl chain for phenyl and cyclohexyl: 2C > 1C (4a > 4 & 4d > 4c)	Mor04m Mor08e ^c	Mass Electronegativity	Appropriate chain length in combination with distinct type of substituted ring are essential for potent activity.
	Length of substituted alkyl chain for 1-adamantyl: 1C > 2C (4e > 4f)	Mor08e G1v H8m	Electronegativity <i>van der Waals</i> volume Mass	Appropriate chain length in combination with distinct type of substituted ring are essential for potent activity.
5	Position of COOH on phenyl ring of 2-amino group: <i>meta</i> > <i>para</i> > <i>ortho</i> (5a > 5b > 5)	H8m Mor04m Mor08e	Mass Mass Electronegativity	5d ^b is the most potent of the series 5. All modifications ↑activity. Equal G1v values were observed among 5 , 5a and 5b . Particular position of COOH substitution on the phenyl ring together with the presence of <i>N</i> -CH ₃ moiety influence the activity (5d > 5a > 5c > 5b > 5).
	CH ₃ substitution on NH group: <i>meta</i> series: ↓activity (5a > 5c) <i>para</i> series: ↑activity (5d > 5b)	H8m Mor04m Mor08e	Mass Mass Electronegativity	Introducing CH ₃ group to <i>para</i> -COOH compound improves activity whereas reduced activity is observed in <i>meta</i> -COOH compound. Equal G1v values were observed among 5c and 5d .

^a Shift from positive to negative value was observed. ^b The most potent of all tested and modified compounds. ^c Shift from negative to positive value was observed.

Table S5 (cont.): Summary of structurally modified compounds (series 1-11)

Series	Comparison	Affected de- descriptors	Related properties	Notes
6	CH ₃ substitution on NH group of <i>m</i> -ketone: NCH ₃ series: ↑activity (6c > 6) NH and NCH ₃ series of COCF ₃ ketone: no effect (6a = 6b)	Mor04m Mor08e H8m G1v	Mass Electronegativity Mass <i>van der Waals</i> volume	6c ^b is the most potent of the series 6. All modifications ↓activity, except 6c . The substitution of CH ₃ on amino group of <i>m</i> -ketone improves activity.
	Type of substituted <i>m</i> -ketone: COCH ₃ > COCF ₃ (6 > 6a)	Mor04m Mor08e H8m	Mass Electronegativity Mass	Substitution with high electronegativity (EN) moiety affects mass (↑Mor04m and ↑H8m) and electronegativity (↓Mor08e) descriptors leading to reduced activity. Equal values of G1v and SIC2 descriptors were observed for 6 and 6a indicating that <i>van der Waals</i> (G1v) and structural information (SIC2) descriptors are not altered by substitution with high EN moiety.
7	CH ₃ substitution on NH group of <i>p</i> -ketone: NCH ₃ of <i>p</i> -COCF ₃ series: ↑activity (7b > 7a) NCH ₃ of <i>p</i> -COCH ₃ series: ↑activity (7c > 7)	Mor04m Mor08e	Mass Electronegativity	7b ^b is the most potent of the series 7. All modifications ↑activity. <i>N</i> -CH ₃ substitution of <i>p</i> -COCF ₃ and <i>p</i> -COCH ₃ improves activity. Marked improved activity was observed in case of 7c .
	Type of substituted <i>p</i> -ketone: COCF ₃ > COCH ₃ (7a > 7)	Mor04m G1v Mor08e H8m	Mass <i>van der Waals</i> volume Electronegativity Mass	Substitution with high EN moiety affects mass (↑Mor04m), electronegativity (↓Mor08e) and <i>van der Waals</i> volume (↑G1v) descriptors and leads to improved activity. The effect found in series 7 is in contrast to series 6 .
8	Position of anilinyll group on phenyl ring: <i>para</i> > <i>meta</i> (8 > 8b)	Mor04m G1v SIC2	Mass <i>van der Waals</i> volume Structural information	8a ^b is the most potent of the series 8. All modifications ↑activity, except 8b . <i>Para</i> -substitution of anilinyll (C ₆ H ₅ N) provides better activity than <i>meta</i> -substitution.
	CH ₃ substitution on NH group: <i>para</i> - and <i>meta</i> -series: ↑activity (8a > 8 and 8c > 8b)	Mor04m G1v	Mass <i>van der Waals</i> volume	Introducing CH ₃ group to the aminophenyl moiety (both <i>para</i> - and <i>meta</i> -) derivatives can markedly improve activity (shift to positive pIC ₅₀ values).
9	Position of substituted aminoquinolone (AQ) ring: 5AQ > 2AQ > 8AQ > 4AQ (9a > 9c > 9 > 9b)	Mor04m Mor08e	Mass Electronegativity	9a ^b is the most potent of the series 9. All modifications ↑activity, except 9b . Marked decrease of Mor08e and Mor04m values were observed in the most potent compound of the series (the 5AQ derivative, 9a). The substituted position of AQ ring affects mass and electronegativity descriptors.

^a Shift from positive to negative value was observed. ^b The most potent of all tested and modified compounds. ^c Shift from negative to positive value was observed.

Table S5 (cont.): Summary of structurally modified compounds (series 1-11)

Series	Comparison	Affected de-descriptors	Related properties	Notes
10	Length of alkyl chain linked between amino group and phenyl ring: 2C > 1C (10 > 10a)	Mor04m H8m G1v	Mass Mass <i>van der Waals</i> volume	All modifications ↓activity. The most potent compound of the series is the prototype 10 ^b . 2C chain length is noted as the most appropriate linker (10).
	CH ₃ substitution on NH group: 1C length: ↑activity (10c > 10a) 2C length: ↓activity (10 > 10b)	Mor04m Mor08e ^c H8m	Mass Electronegativity Mass	Substitution of CH ₃ moiety on the 2-amino group can improve or reduce activity of the compound depending on the length of linker chain.
11	Position of diOMe on the phenyl ring : 2,3-position > 3,4-position (11b > 11)	Mor08e ^a G1v	Electronegativity <i>van der Waals</i> volume	11b ^b is the most potent of the series 11. All modifications ↑activity. Distinct position of diOMe substitution on the phenyl ring is required for preferable activity.
	CH ₃ substitution on NH group: 2,3-diOMe: ↓activity (11b > 11c) 3,4-diOMe: ↑activity (11a > 11)	Mor08e ^c Mor04m H8m	Electronegativity Mass Mass	Substitution of CH ₃ moiety on the 2-amino group can improve or reduce activity of the compound depending on the position of diOMe substitution.

^a Shift from positive to negative value was observed. ^b The most potent of all tested and modified compounds. ^c Shift from negative to positive value was observed.

PREDICTION OF STRUCTURALLY MODIFIED COMPOUNDS USING CONSTRUCTED QSAR MODEL: A DETAILED DISCUSSION

The effect of substituted alkyl chain length on the amino group was observed in modified compounds series **2** in which all of them exhibited higher activity than the parent compound **2**, except for compound **2c**. It was found that the shorter substituted alkyl chain provided the better activity than the long chain alkyl group *via* an increased *van der Waals* volume (G1v) but mostly with decreased mass (Mor04m) and electronegativity (Mor08e) as seen in **2b** > **2a** > **2**, Table S1. Particularly, *N,N*-dimethylaminoquinone **2f** was found to be the most potent compound (Table S4). This could be due to high G1v value of 0.175 that gave 1st component symmetry directional WHIM index deriving from dimethyl substituents on the amino moiety. Furthermore, the additional CH₃ substituent at amino group gave tertiary amines with reduced activity when compared to compounds with the same length of substituted alkyl chain (**2b** > **2e**, **2a** > **2d** and **2** > **2c**, Table S4).

The notable enhanced effects of ring substituted at the amino group was observed in modified compounds series **3** in which the replacement of phenyl ring of **3** by 1-adamantyl and cyclohexyl rings can markedly increase the activity of the inactive compound (**3**) to moderately actives **3a** and **3b**, respectively. Furthermore, the substitution of various quinolines at 2-amino position in modified series **9** provided more potent compounds as compared to the *N*-alkyl chain and *N*-phenyl substitutions in series **2** and **3**, respectively. Compound **9a** was predicted to be the most potent compound of the series **9**, which indicated the substitution at position 5 of quinoline ring to be the most appropriate substitution. It was noticed that all aminoquinoline derivatives in series **9**, except for **9a**, possess equivalent G1v values of 0.179 (Table S1). The exceptional activity of 5-aminoquinoline compound **9a** may be due to its decreased mass (Mor04m), electronegativity (Mor08e) and *van der Waals* volume (G1v) but increased neighborhood symmetry of 2-order (SIC2).

The effects of *ortho*-/*meta*-/*para*-carboxyl (COOH) and acetyl (COCH₃) substituted on amino phenyl ring along with the presence of additional methyl (CH₃) substituent on 2-amino group of 1,4-naphthoquinone core were investigated as shown in modified compounds series **5**, **6**, and **7**. Interestingly, the addition of CH₃ moiety can either improve or reduce the activity of the compound depending on the position of substituted carboxyl (COOH) and acetyl (COCH₃) groups, Table S4. For carboxyl compounds (series **5**), compound **5d** exhibited the best activity (moderately active, pIC₅₀ -0.329) affording 1.26 folds more potent than the reference drug, ketoconazole (pIC₅₀ -0.415) which indicated the *para*-carboxyl substitution on the phenyl ring together with the insertion of methyl moiety to 2-amino group as the most appropriate modification of the series. For acetyl compounds (series **6** and **7**), the *meta*-substituted compound (**6**) exhibited more potent activity than that of the *para*-substituted compound (**7**). In addition, introducing the methyl moiety to the 2-amino group of the compound can markedly improve activity of both *meta*- and *para*-compounds (**6c** > **6**: 1.67 folds and **7c** > **7**: 2.73 folds, respectively). In addition, the effect of replacing the acetyl (COCH₃) moiety with the trifluoroacetyl (COCF₃) moiety were investigated. The contrast effects were observed in *meta*- (**6**) and *para*- (**7**) series. Introducing the COCF₃ moiety to the compound increased activity of the *para*-compound (**7a** > **7**: 1.47 folds) whereas vice versa effect was observed in case of the *meta*-compound (**6** > **6a**: 1.83 folds). Moreover, no change was observed when methyl group was added to 2-amino group of *meta*-trifluoroacetyl compound **6a** (**6a** = **6b**) but improved activity was obtained in case of the *para*-trifluoroacetyl compound **7a** (**7b** > **7a**: 2.28 folds).

It was found that the length of alkyl chain linking between 2-amino group and the terminal phenyl ring influences the activity of the compounds. Considering the structural modifications of compound series **10**, the improved activity cannot be found in the modified compounds (i.e., **10a**, **10b** and **10c**), however, the parent compound **10** with 2C chain length linker was observed

to be the most appropriate chain length providing the best activity. Moreover, the effect of additional methyl substituent at 2-amino group on activity of compounds was dependent on the length of the linker chain (Table S4). The effects of diOMe substituents on the terminal phenyl ring were observed along with the presence of additional methyl substitution at 2-amino group (series **11**). All modified compounds in this series were predicted to exhibit improved activity (moderately to weakly active) as compared to their parent compound **11** (inactive). It was found that more potent activity can be achieved by 2,3-diOMe substitution (**11b**) rather than by 3,4-diOMe substitution (**11**). The enhanced effect may be governed by the decreasing of electro-negativity descriptor value (Mor08e: **11** = 0.295, **11b** = -0.222) in which the shift from positive to negative value was observed for 2,3-diOMe substituted compound (**11b**). Substitution by methyl moiety on the 2-amino group of 3,4-diOMe compound (**11**) gave compound **11a** with the improved activity *via* marked decrease of Mor04m (2.00 folds), and marked increase of Mor08e (2.13 folds) and H8m (2.84 folds) descriptor values as compared to the parent compound **11**. In contrast, the deteriorate effect of methyl substitution on the 2-amino group was observed in case of the most potent 2,3-diOMe compound (**11b**) was converted to *N*-methyl compound **11c**. In this regard, a pronounced increase of Mor08e value of **11c** was observed (Mor08e: **11b** = -0.222 and **11c** = 0.326) along with an increase of H8m (3.17 folds) and a decrease of Mor04m (2.68 folds).