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Discovery of Aporphine Analogues as Potential Antiplatelet and Antioxidant Agents: Design, Synthesis, Structure–Activity Relationships, Biological Evaluations, and in silico Molecular Docking Studies

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To explore the potential of aporphine alkaloids, a novel series of functionalized aporphine analogues with alkoxy (OCH_3, OC_2H_5, OC_3H_7) functional groups at C1/C2 of ring A and an acyl ($COCH_3$ and COPh) or phenylsulfonyl (SO_2Ph and $SO_2C_6H_4$-3-CH_3) functionality at the N6 position of ring B of the aporphine scaffold were synthesized and evaluated for their arachidonic acid (AA)-induced antiplatelet aggregation inhibitory activity and 2,2-diphenyl-1-picrylhydrazyl (DPPH) free-radical-scavenging antioxidant activity, with acetylsalicylic acid and ascorbic acid as standard references, respectively. The preliminary structure–activity relationship related to AA-induced platelet aggregation inhibitory activity results showed that the aporphine analogues 1-[1,2,9,10-tetramethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]quinolin-6(5*H*)-yl]ethanone and 1-[2-(benzyloxy)-1,9,10-trimethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]quinolin-6(5*H*)-yl]ethanone to be the best compounds of the series. Moreover, the DPPH free-radical-scavenging antioxidant activity results demonstrated that the aporphine analogues 1,2,9,10-tetramethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 2-ethoxy-1,9,10-trimethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 1-ethoxy-2,9,10-trimethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 2,9,10-trimethoxy-6-(methylsulfonyl)-1-propoxy-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, and 1-(benzyloxy)-2,9,10-trimethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo-[*de*,*g*]quinoline were the best compounds of the series. Moreover, in silico molecular docking simulation studies of the active analogues were also performed.

Introduction

1,2,3,4-Tetrahydroisoquinoline substructure **1** is present in the basic tetracyclic framework of aporphine alkaloids **2**. A large number of aporphine alkaloids have been isolated from several plant species (e.g., Hernandiaceae, Lauraceae, Annonaceae, etc.) and have been synthesized by several routes.[1] Both natural and synthetic aporphine alkaloids display a wide range of pharmacological activities and also serve as leads for the development of potential drug-discovery scaffolds. For example, natural/synthetic aporphines have been identified as antimicrobial,[2a] antiviral,[2b,c] and acetyl cholinesterase inhibitors;[2d] antimalarial agents;[2e,f] central nervous system receptor ligands;[1c,2h] anti-Alzheimer agents;[1c,2d–f,g,h] and potent dopamine D1/D2 agonists.[2i] Additionally, their characteristic tetracyclic motif with different levels of oxidation on both aromatic rings results in a diverse range of interesting biological activities, including antimalarial,[3a] serotonergic,[3b] anticancer,[3c] vasorelaxing[3d] and cytotoxic activities.[3e] Moreover, literature reports reveal that natural and semisynthetic aporphines **3**–**14** show excellent antioxidant[4] and antiplatelet activities[5] (Figure 1).

On the other hand, cyclic/acyclic ester/amide analogues **15** and sulfonamide analogues **16** display promising antioxidant activities (e.g., exifone, 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one, benzo[1,3]oxazine, benzo[1,4]oxazine analogues, etc.)[6] and antiplatelet activities (e.g., acetylsalicylic acid (Aspirin), tirofiban, sulfinpyrazone, clopidogrel, etc.).[7]

Thus, we anticipated that the combination of these two moieties, that is, **3**–**14** and **15**–**16**, in part or in their entire molecular architectures, might display promising antiplatelet and antioxidant activities; we designed novel aporphine analogues **17** and **18** (Figure 2). Moreover, a literature survey revealed that there is no detailed systematic study of the structure–activity relationship (SAR) of synthetic aporphines having an amide/sulfonamide substructure as antiplatelet and antioxidant agents until now.

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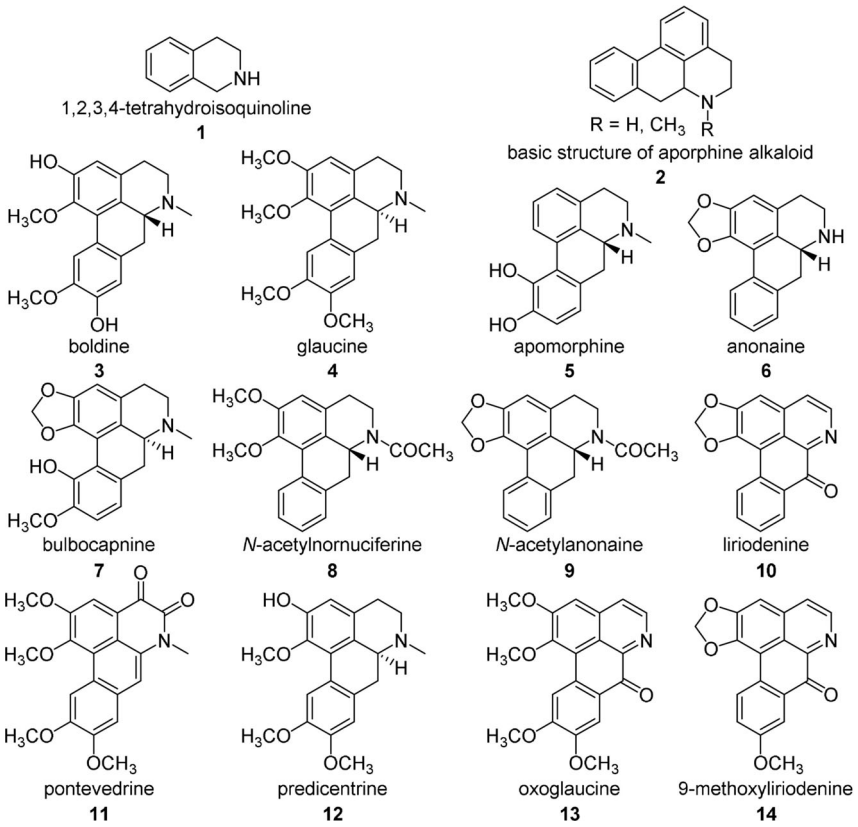


Figure 1. Basic structures of aporphine alkaloids **2**, aporphine alkaloids **3**–**7** having antioxidant activity, and aporphine alkaloids **8**–**14** having antiplatelet activity.

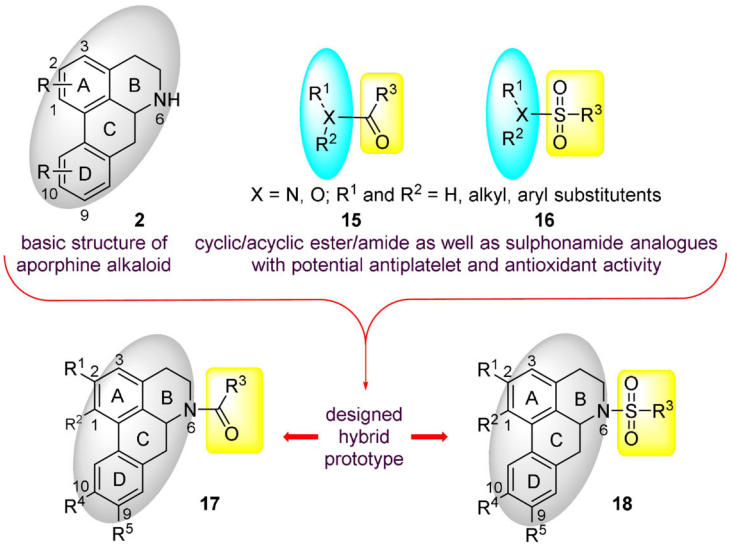


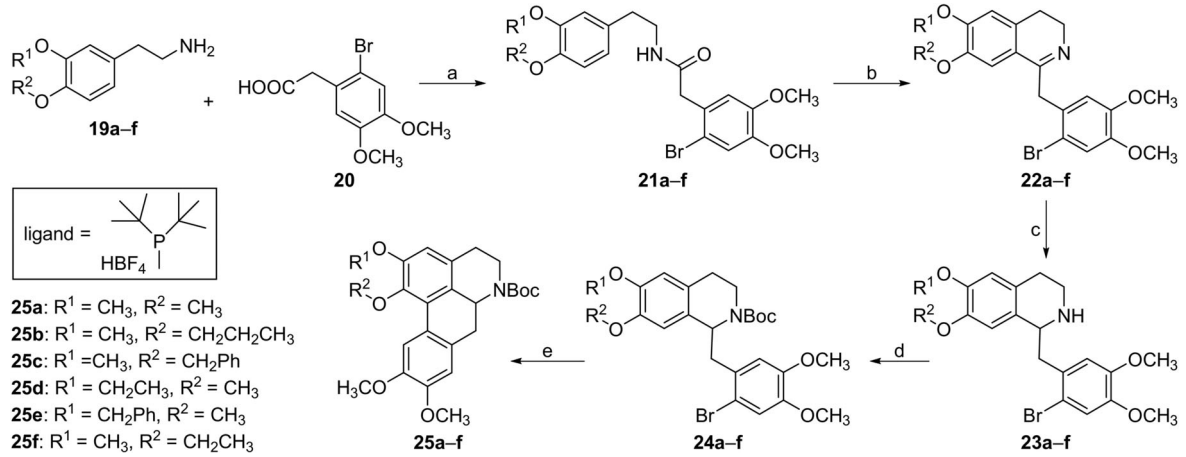
Figure 2. Designed strategy and the basic structures of aporphine alkaloids **2**, functionalized amides **15**, functionalized sulfonamides **16**, and designed aporphine–amide/sulfonamide hybrid prototypes **17** and **18**.

Therefore, in our search for potent antiplatelet/antioxidant agents, we report the synthesis of aporphines **27a**–**s** as analogues of prototypes **17** and **18** having structural modifications at C1/C2 of ring A and amide/sulfonamide functionality at the N6 position of ring B along with their SAR studies with respect on their preliminary arachidonic acid (AA)-induced platelet aggregation inhibitory activity and 2,2-diphenyl-1-picrylhydrazyl (DPPH) free-radical-scavenging antioxidant activity taking ascorbic acid and acetylsalicylic acid as standard drug references, respectively. To the best of our knowledge, this is the first report of the synthesis, SAR, and antiplatelet and antioxidant activity of novel racemic aporphine analogues **27a**–**s**. We also report in silico molecular docking simulation studies of the active analogues.

Results and Discussion

In our endeavor to develop non-peptide-based antiplatelet agents; we recently reported that the inhibition of cyclooxygenase-1 (COX-1) was the key target in the development of novel platelet aggregation inhibitors.[8a] As acetylsalicylic acid, tirofiban, sulfinpyrazone, and clopidogrel are well-established potent platelet-aggregation inhibitors that contain amide/sulfonamide moieties and as natural/semisynthetic aporphine analogues **3**–**7** were reported to show promising antioxidant activities, we envisaged that aporphines having these scaffolds would also show potent activities.

Several routes have been reported for the synthesis of aporphines and related alkaloids and similar scaffolds.[8b–d] There-



Scheme 1. Reagents and conditions: a) 1,1′-carbonyldiimidazole, THF, RT, 20 h, 72–84%; b) PCl_5, CH_2Cl_2, 0 °C to RT, 12 h; c) $NaBH_4$, MeOH, 0 °C, 5 h; d) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, RT, 12 h, 70–83%; e) $Pd(OAc)_2$, ligand, K_2CO_3, $(CH_3)_3CCOOH$, DMSO, 130 °C, 18 h, 73–92%.

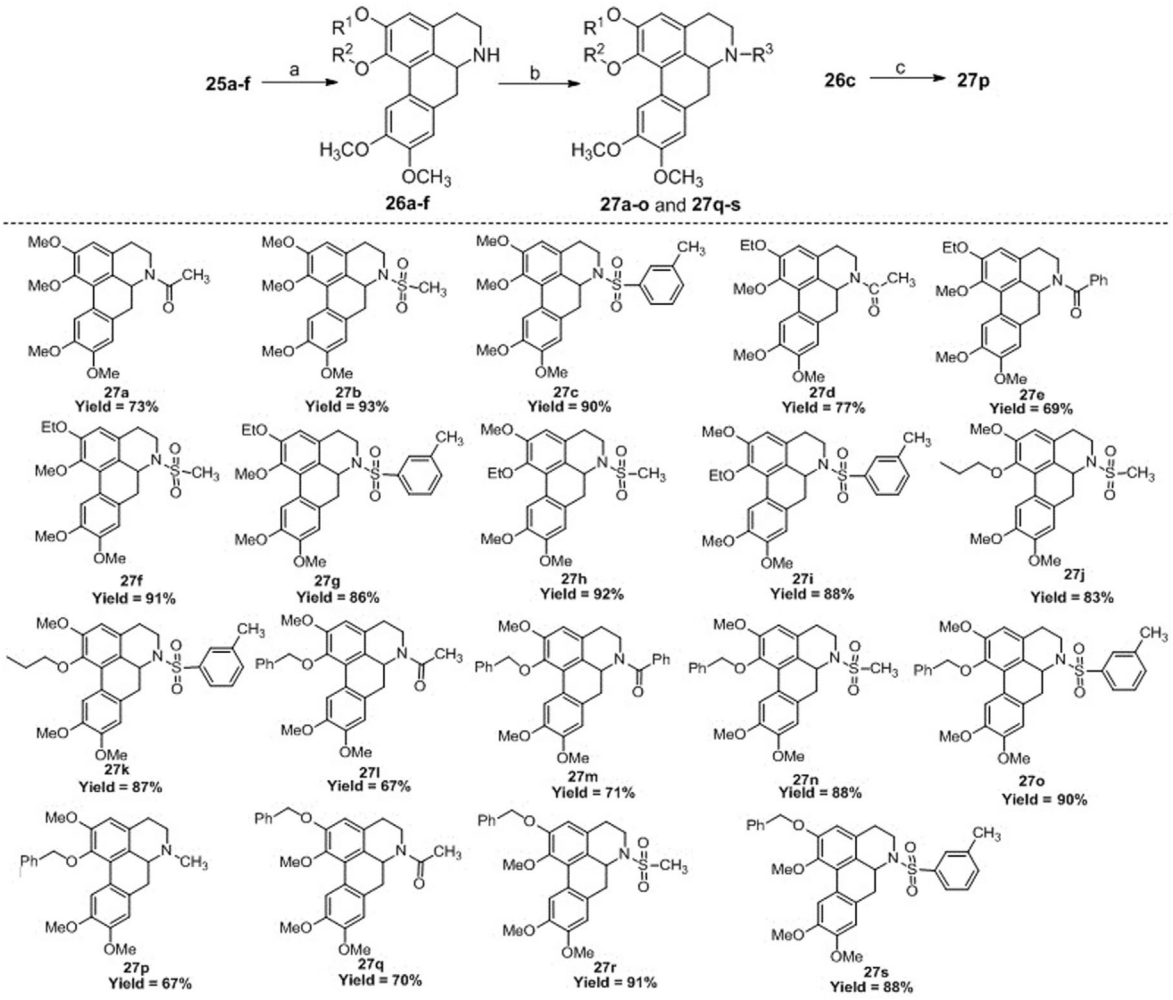
fore, novel aporphine analogues **27a–s** having structural modifications at C1/C2 of ring A and at the N6 position of ring B were prepared by using reported procedures[8e,f] (Schemes 1 and 2). The coupling of functionalized phenethylamine analogues **19a–f** with 2-(2-bromo-4,5-dimethoxyphenyl)acetic acid (**20**) under standard peptide-coupling conditions gave amides **21a–f**. Amides **21a–f** were subjected to the Bischler–Napieralski reaction[9] to afford cyclized imines **22a–f**, which, without further purification, were subjected to $NaBH_4$ reduction to furnish secondary amines **23a–f**. Protection of these amines with a *tert*-butoxycarbonyl (Boc) group furnished C1- and C2-functionalized N6 carbamates **24a–f**. Finally, *N*-Boc-protected aporphine analogues **25a–f** (up to 94% yield) were prepared by Pd-catalyzed direct biaryl coupling methodology (Scheme 1).[10] *N*-Carbamate (i.e., *N*-Boc) aporphine analogues **25a–f** were used as the key precursors for the synthesis of novel aporphine analogues **27a–s** (Scheme 2). Hence, the synthesis of N6 amide/sulfonamide analogues **27a–o** and **27q–s** was achieved by deprotection of the Boc group[8e] of **25a–f** by using anhydrous $ZnBr_2$ and subsequent N-alkylation with different alkyl/aryl halides. In addition, the subsequent reductive amination of secondary amine **26c** with formaldehyde afforded *N*-methylated aporphine analogue **27p** (Scheme 2). All of these compounds were well characterized by using ^{1}H NMR, ^{13}C NMR, and FTIR spectroscopy and high-resolution (HR) ESI-MS. As expected, the NMR spectral data (^{1}H NMR and ^{13}C NMR) of the *N*-acetyl analogues revealed a mixture of rotamers (see the Experimental Section).

Synthesized novel aporphines **27a–s** having alkoxy (OCH_3, OC_2H_5, OC_3H_7) functional groups at C1/C2 of ring A along with acyl ($COCH_3$ and COPh)/phenylsulfonyl (SO_2Ph and $SO_2C_6H_4$-3-CH_3) functionality at the N6 position of ring B were evaluated for their arachidonic acid (AA)-induced antiplatelet aggregation inhibitory activity as well as their DPPH radical-scavenging antioxidant activity taking acetylsalicylic acid and ascorbic acid as standard references, respectively, by using a reported procedure[11,12] (Tables 1 and 2).

As depicted in Table 1, initially, compounds **27a**, **27b**, and **27c** having OCH_3 substituents at C1 and C2 of ring A and *N*-$COCH_3$, *N*-SO_2CH_3, and *N*-$SO_2C_6H_4$-3-CH_3 substituents in ring B, respectively, were prepared; of these compounds, **27a** (IC_{50} = 20.08 ± 0.22 μg mL^{-1}) displayed higher AA-induced platelet aggregation inhibitory activity than acetylsalicylic acid (IC_{50} = 21.34 ± 1.09 μg mL^{-1}; Table 1, entry 1). Changing the *N*-$COCH_3$ group to an *N*-SO_2CH_3 or *N*-$SO_2C_6H_4$-3-CH_3 group further decreased the activity (Table 1, entries 2 and 3). Then, higher homologues of **27a–c**, that is, **27d** (IC_{50} = 29.78 ± 0.31 μg mL^{-1}), **27f**, and **27g** having an ethoxy group at the C2 position were assessed, and we observed a similar decrease in the antiplatelet activity upon changing the N-substituents from an acetyl group to either a sulfonyl or (3-methylphenyl)sulfonyl group (Table 1, entries 4, 6, and 7). Although *N*-benzoyl analogue **27e** (IC_{50} = 25.83 ± 0.26 μg mL^{-1}) displayed better antiplatelet activity than **27d**, **27f**, and **27g**, its antiplatelet activity was similar to that of acetylsalicylic acid (Table 1, entry 5). The platelet aggregation inhibitory activities of compounds **27h** (IC_{50} = 101.83 ± 1.08 μg mL^{-1}), **27i** (IC_{50} = 33.37 ± 0.34 μg mL^{-1}), **27j** (IC_{50} = 37.71 ± 0.38 μg mL^{-1}), and **27k** (IC_{50} = 40.00 ± 0.48 μg mL^{-1}) having an *N*-sulfonyl substituent and an ethoxy/propoxy group at the C2 position were drastically lower than that of parent analogue **27a** having an *N*-acetyl group (Table 1, entries 8–11).

As we did not observe any noticeable improvement in the activity upon increasing the length of the alkyl chain, we introduced aromatic moieties at both the C1 and C2 positions. So, we prepared **27l–p** and **27q–s** having benzyloxy groups at C1/C2 of ring A and an *N*-acetyl, *N*-benzoyl, *N*-arylsulfonyl, or *N*-methylsulfonyl group in ring B as aporphine analogues. As expected, **27l** showed better AA-induced platelet aggregation inhibitory activity than **27m--o**; moreover, the IC_{50} value of **27p** having an *N*-CH_3 group (IC_{50} = 27.83 ± 0.29 μg mL^{-1}), the reduced form of **27l**, was also promising relative to that of acetylsalicylic acid (Table 1, entries 12–16).

Thus, it can be inferred that substitution of the *N*-acetyl group with an *N*-benzoyl group does not have a beneficial effect on antiplatelet activity. Analogue **27m** (IC_{50} = 58.13 ± 0.77 μg mL^{-1}), having two phenyl moieties, exhibited lower activity than acetyl analogue **27l**. Aporphine analogues **27q–s**,



Scheme 2. Reagents and conditions: a) $ZnBr_2$, CH_2Cl_2, RT, 24 h; b) R^3Cl [$R^3 = COCH_3$, COPh, SO_2CH_3, $SO_2C_6H_4$-3-CH_3], Et_3N, CH_2Cl_2, 0 °C, 3 h, 69–93 %; c) aq. HCHO, $NaBH(OAc)_3$, CH_2Cl_2, RT, 24 h, 67 %.

having a benzyloxy group at the C2 position and an *N*-acetyl group, also follows the same trend, that is, **27 q** ($IC_{50} = 21.29 \pm 0.25\ \mu g\,mL^{-1}$) was as active as acetylsalicylic acid and more active than its *N*-sulfonyl counterparts (Table 1, entries 17 and 18).

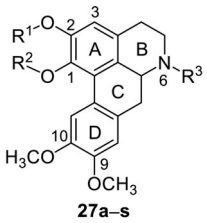
Overall, on the basis of the above SAR study, two compounds, that is, **27 a** and **27 q**, having OCH_3 and OCH_2Ph substituents at C1, a OCH_3 substituent at the C2 position of ring A, and an *N*-acetyl group, were the most active compounds of the series and displayed greater antiplatelet activity than acetylsalicylic acid. It can be interpreted that the *N*-acetyl analogue of aporphines (i.e., compounds **27 a**, **27 d**, **27 l**, and **27 q**) showed better platelet aggregation inhibitory activity than the *N*-sulfonamide analogues. However, the position of the alkoxy substituent at C1 and C2 of ring A is also responsible for the antiplatelet activity. Similarly, the *N*-methyl group of aporphine analogue **27 p** further reduced the antiplatelet activity.

Synthesized novel racemic aporphines **27 a**–**s** were also screened for their preliminary antioxidant activity by using the DPPH free-radical-scavenging antioxidant activity assay taking ascorbic acid as a standard reference by using a reported protocol.[13] The results are shown in Table 1.

DPPH is a stable free radical that can easily be converted into a stable molecule after the acceptance of an electron or hydrogen radical. It is well documented that the DPPH radical-scavenging antioxidant activity assay proceeds through a single-electron-transfer (SET) or hydrogen-atom-transfer (HAT) mechanism.[12a–c] The DPPH molecule shows a strong absorption band at $\lambda = 515$ nm in MeOH solution with a deep-purple color and having an odd electron configuration. The deep-purple color of the MeOH medium containing DPPH changes to yellow in the presence of free-radical scavengers.[12d,e] Quenching of the DPPH free radical can be correlated with the structural architecture of the quenching molecule, and steric hindrance, rigidity, and electron density are key factors that may facilitate access of this molecule to the radical site of DPPH, thus, to enhance the antioxidant activity.[12f,g]

Initially, in vitro antioxidant screening of novel aporphine analogues **27 a**–**c** having OCH_3 substituents at the C1/C2 positions of ring A and an *N*-acetyl, *N*-sulfonyl, or *N*-(3-methylphe-

Table 1. In vitro AA-induced platelet aggregation inhibitory activity and in vitro DPPH radical-scavenging antioxidant activity of synthesized aporphine analogues **27a–s**.



27a–s

Entry	Compound	R^1	R^2	R^3	IC_{50} [μg mL^{-1}] Antiplatelet[a,b]	Antioxidant[c,d]
1	**27a**	CH_3	CH_3	$COCH_3$	**20.08±0.22**	70.69±0.68
2	**27b**	CH_3	CH_3	SO_2CH_3	31.19±0.29	**10.18±0.10**
3	**27c**	CH_3	CH_3	$SO_2C_6H_4$-3-CH_3	57.29±0.74	21.97±0.22
4	**27d**	CH_2CH_3	CH_3	$COCH_3$	29.78±0.31	30.08±0.34
5	**27e**	CH_2CH_3	CH_3	COPh	25.83±0.26	88.36±0.79
6	**27f**	CH_2CH_3	CH_3	SO_2CH_3	44.97±0.67	**5.87±0.07**
7	**27g**	CH_2CH_3	CH_3	$SO_2C_6H_4$-3-CH_3	103.64±1.01	103.11±1.01
8	**27h**	CH_3	CH_2CH_3	SO_2CH_3	101.83±1.08	**7.08±0.10**
9	**27i**	CH_3	CH_2CH_3	$SO_2C_6H_4$-3-CH_3	33.37±0.34	96.13±0.74
10	**27j**	CH_3	$CH_2CH_2CH_3$	SO_2CH_3	37.71±0.38	**5.13±0.07**
11	**27k**	CH_3	$CH_2CH_2CH_3$	$SO_2C_6H_4$-3-CH_3	40.00±0.48	29.31±0.30
12	**27l**	CH_3	CH_2Ph	$COCH_3$	28.81±0.37	**11.71±0.14**
13	**27m**	CH_3	CH_2Ph	COPh	58.13±0.77	23.14±0.29
14	**27n**	CH_3	CH_2Ph	SO_2CH_3	71.88±0.08	**4.36±0.09**
15	**27o**	CH_3	CH_2Ph	$SO_2C_6H_4$-3-CH_3	78.67±0.88	44.87±0.36
16	**27p**	CH_3	CH_2Ph	CH_3	27.83±0.29	19.63±0.22
17	**27q**	CH_2Ph	CH_3	$COCH_3$	**21.29±0.25**	41.58±0.39
18	**27r**	CH_2Ph	CH_3	SO_2CH_3	41.97±0.44	14.53±0.31
19	**27s**	CH_2Ph	CH_3	$SO_2C_6H_4$-3-CH_3	96.02±0.97	50.08±0.45
20	acetylsalicylic acid	–	–	–	**21.34±1.09**	–
21	ascorbic acid	–	–	–	–	**4.57**

[a] Platelets were incubated along with either a tested compound or 0.5% DMSO at 37 °C for 60 s, and then AA (100 μM) was added to accelerate aggregation. Acetylsalicylic acid was a positive control. Values are expressed as the mean of six separations. [b] The data represent the mean of three independent determinations. [c] Results are expressed as mean±SD ($n=3$). [d] DPPH radical-scavenging activities are expressed as IC_{50} concentrations of the compounds required to inhibit 50% of the radicals and the maximum inhibition values, and the positive control for the DPPH assay was ascorbic acid. Values in boldface indicate compounds with high activity.

nyl)sulfonyl group at the N6 position were assessed, and it was observed that **27a** ($IC_{50}=70.69\pm0.68$ μg mL^{-1}) having OCH_3 substituents at both the C1/C2 positions along with an *N*-acetyl group displayed lower potency than ascorbic acid ($IC_{50}=4.57$ μg mL^{-1}; Table 1, entry 1). However, **27b** ($IC_{50}=10.18\pm0.10$ μg mL^{-1}) having an *N*-sulfonyl group showed significantly higher antioxidant activity than **27a** (Table 1, entry 2). Upon changing to an *N*-arylsulfonyl group, that is, compound **27c** ($IC_{50}=21.97\pm0.22$ μg mL^{-1}), a further decrease in the antioxidant activity was observed (Table 1, entry 3).

Similar trends were observed upon analyzing **27d–k** having ethoxy/propoxy groups at the C1/C2 positions along with an *N*-acetyl, *N*-benzoyl, *N*-methylsulfonyl, or *N*–arylsulfonyl group at the N6 position (Table 1, entries 4–11). Whereas analogues **27f** ($IC_{50}=5.87\pm0.07$ μg mL^{-1}), **27h** ($IC_{50}=7.08\pm0.10$ μg mL^{-1}), and **27j** ($IC_{50}=5.13\pm0.07$ μg mL^{-1}) displayed excellent antioxidant potency similar to that of the standard drug (Table 1, entries 6, 8, and 10), other analogues, as in compounds **27d** ($IC_{50}=30.08\pm0.34$ μg mL^{-1}), **27e** ($IC_{50}=88.36\pm0.79$ μg mL^{-1}), **27g** ($IC_{50}=103.11\pm1.01$ μg mL^{-1}), **27i** ($IC_{50}=96.13\pm0.74$ μg mL^{-1}), and **27k** ($IC_{50}=29.31\pm0.30$ μg mL^{-1}), displayed poor potency (Table 1, entries 4–5, 7, 9 and 11).

We were also interested to study the effect of the aromatic ring at the C1/C2 positions of ring A. Therefore, we prepared aporphine analogues **27l–s** having an *N*-acetyl, *N*-benzoyl, *N*-methylsulfonyl, or *N*-arylsulfonyl group at the N6 position (Table 1, entries 12–19). Compound **27l** ($IC_{50}=11.71\pm0.14$ μg mL^{-1}) having a benzyloxy group at the C2 position and an *N*-acetyl group showed promising antioxidant activity. However, changing the acetyl group to a methylsulfonyl group at the N6 position had a profound effect on the antioxidant activity, as observed in the case of **27n** ($IC_{50}=4.36\pm0.09$ μg mL^{-1}), which showed higher activity than ascorbic acid ($IC_{50}=4.57$ μg mL^{-1}). Thus, **27n** was found to be the best compound of the series. The activity decreased if a benzoyl or arylsulfonyl group was introduced at the N6 position [**27m**, $IC_{50}=(23.14\pm0.29)$ μg mL^{-1}; **27o**, $IC_{50}=(44.87\pm0.36)$ μg mL^{-1}; Table 1, entries 13 and 15]. In addition, the tertiary amine analogue, that is, *N*-methylaporphine **27p** ($IC_{50}=19.63\pm0.22$ μg mL^{-1}), exhibited lower antioxidant activity (Table 1, entry 16). We did not observe an incremental effect in the activity upon reversing the position of the aromatic substituent at the C1/C2 positions, as in compounds **27q–s** (Table 1, entries 17–19). However, **27r** ($IC_{50}=14.53\pm0.31$ μg mL^{-1}) having an *N*-SO_2CH_3 group showed

promising antioxidant activity relative to **27q** ($IC_{50}=41.58\pm0.39\ \mu g\,mL^{-1}$) and **27s** ($IC_{50}=50.08\pm0.45\ \mu g\,mL^{-1}$).

On the basis of the above results, it was observed that the *N*-methylsulfonyl substituent in aporphine analogues **27b**, **27f**, **27h**, **27j**, and **27n** played a crucial role in antioxidant activity, and these compounds were the most active compounds of the series. Analogues **27c**, **27g**, **27i**, **27k**, **27o**, and **27s** having an *N*-arylsulfonyl group and aporphine analogues **27a**, **27d**, **27e**, **27l**, **27m**, and **27q** having an *N*-acetyl or *N*-benzoyl group displayed lower antioxidant activity. Hence, it can be speculated that the higher electronegativity of the sulfur atom in the *N*-methylsulfonyl-containing aporphine analogues, which is able to accumulate electron density (the *N*-arylsulfonylaporphines have lower electron density owing to the presence of the electron-withdrawing aryl substituent despite the presence of the electron-donating methyl substituent), restricts delocalization of the bonds; as a result, the free electrons are not available to quench the DPPH radical, and this might be a plausible reason for the good antioxidant activity.

We then performed in silico molecular docking simulation studies by exploring the binding interactions, and we predicted the binding affinities of selected synthesized aporphine analogues that were active, in addition to those of the reference standard, acetylsalicylic acid, and ascorbic acid, with the protein targets [2OYE, i.e., indomethacin-(*R*)-α-ethylethanolamide bound to cyclooxygenase-1, and 3MNG, i.e., dithiothreitol bound with human peroxiredoxin 5] (Tables 2 and 3). The binding affinities were measured as the "total" docking score. The reliability of the docking program parameters was measured in terms of root-mean-square-deviation (RMSD) values in between the co-crystallized ligand and the redocked poses. The RMSD values were found to be 0.6563 and 1.1420 for the 2OYE and 3MNG proteins, respectively, which suggested that the docking program parameters could be used for docking of our synthesized compounds (Figure 3).

With the insight obtained from the binding interaction of the co-crystallized ligand, we further docked and analyzed the binding interaction of compounds **27a** and **27q** (Figure 4). These compounds exhibited better platelet aggregation inhibition activity than acetylsalicylic acid (a standard reference used as a platelet aggregation inhibitor). The docking results for compound **27q** showed a high binding affinity represented by a total docking score of 7.4851 (Figure 4a). Compound **27q** forms H-bonds to the polar, uncharged, and nucleophilic Ser-530 (2.31 Å) and π–π interactions with hydrophobic Tyr-355. In the docking pose, the binding-site residues within a radius of 3 Å from the bound compound are aliphatic and hydrophobic Ile-89, Ile-517, Ile-523, Leu-93, Leu-352, Leu-359, Leu-531, Val-116, Val-349, Ala-527, and Gly-526; aromatic and hydrophobic Tyr-348, Tyr-355, Tyr-385, Phe-381, Phe-518, and Trp-387; basic, polar, and positively charged Arg-120; and polar, uncharged, and nucleophilic Ser-353 and Ser-530.

Similarly, the docking results for compound **27a** also showed good binding affinity in the total score of 5.9304 and a H-bond length of 1.71 Å to polar, uncharged, and nucleophilic Ser-530 (Figure 4b). The compound also displayed a π–π interaction with hydrophobic Tyr-355 (aromatic, hydrophobic).

Table 2. Comparison of the binding affinities of active aporphine analogues **27a** and **27q** with that of acetylsalicylic acid as the standard drug reference against antiplatelet target protein (PDB ID: 2OYE).

Compound	Total docking score	Residues in the binding site within 3 Å of ligand	Residues involved in H-bonds
IM8	10.5285	Ile-89, Val-116, Arg-120, Val-349, Tyr-355, Ser-353, Leu-384, Phe-518, Met-522, Ile-523, Glu-524, Gly-526, Ala-527, Ser-530	Glu-524 (2.04 Å), Tyr-355 (2.12 Å), Trp-387 (3.26 Å)
27a	5.9304	Tyr-348, Val-349, Leu-352, Ser-353, Tyr-355, Leu-359, Tyr-385, Trp-387, Ile-517, Phe-518, Ile-523, Ala-527, Ser-530, Leu-531	Ser-530 (1.71 Å), Tyr-355 (π–π)
27q	7.4851	Ile-89, Leu-93, Val-116, Arg-120, Tyr-348, Val-349, Leu-352, Ser-353, Tyr-355, Leu-359, Phe-381, Tyr-385, Trp-387, Ile-517, Phe-518, Ile-523, Gly-526, Ala-527, Ser-530, Leu-531	Ser-530 (2.31 Å), Tyr-355 (π–π)
acetylsalicylic acid	4.9713	Tyr-348, Val-349, Leu-352, Phe-381, Leu-384, Tyr-385, Trp-387, Gly-526, Ala-527, Ser-530	Ser-530 (1.84 Å), Tyr-355 (2.08 Å)

Table 3. Comparison of the binding affinities of promising antioxidant-active aporphine analogues with that of ascorbic acid as the standard drug against an antioxidant target protein (PDB ID: 3MNG).

Compound	Docking score	Residues in the binding site within 3 Å of the ligand	Residues involved in H-bonds
DID	3.5321	Pro-40, Thr-44, Pro-45, Gly-46, Cys-47, Phe-120, Arg-127, Thr-147	Arg-127 (1.96 Å), Thr-44 (2.62 Å)
27b	2.9735	Pro-40, Pro-45, Gly-46, Lys-49, Leu-116, Phe-120, Arg-127, Thr-147, Leu-149	Arg-127 (2.43, 2.65 Å)
27f	4.4967	Pro-40, Pro-45, Gly-46, Phe-120, Arg-127, Thr-147, Leu-149	Gly-46 (3.71 Å)
27h	3.9514	Pro-40, Thr-44, Pro-45, Gly-46, Lys-49, Leu-116, Phe-120, Arg-127, Thr-147, Leu-149	Arg-127 (2.59 Å)
27j	5.1878	Pro-40, Pro-45, Gly-46, Leu-116, Ile-119, Phe-120, Arg-127, Thr-147, Leu-149	Arg-127 (2.62, 2.12 Å),Thr-147 (1.98 Å)
27l	4.6290	Pro-45, Gly-46, Lys-49, Arg-127, Thr-147, Gly-148, Leu-149	Gly-46 (2.55 Å), Lys-49 (2.31 Å)
27n	4.7335	Pro-45, Gly-46, Lys-49, Phe-120, Arg-127, Thr-147, Gly-148, Leu-149	Gly-46 (2.53 Å), Lys-49 (2.26 Å)
ascorbic acid	4.2924	Pro-40, Thr-44, Pro-45, Gly-46, Cys-47, Leu-116, Arg-127, Thr-147	Thr-44 (1.90 Å), Gly-46 (2.06 Å), Thr-147 (1.97 Å)

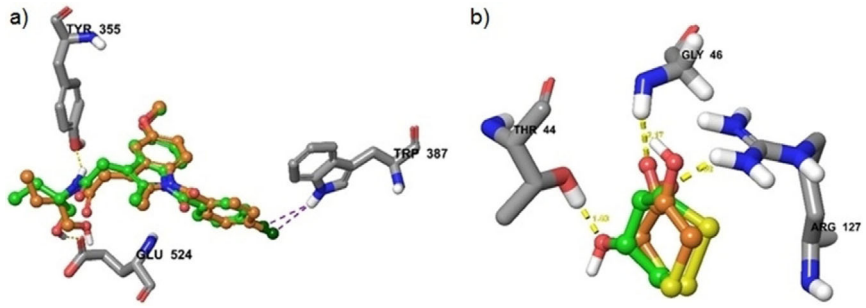


Figure 3. Protein targets a) 2OYE and b) 3MNG having docking scores, that is, RMSDs, of 0.6563 and 1.1420 for co-crystallized IM8 and DID, respectively.

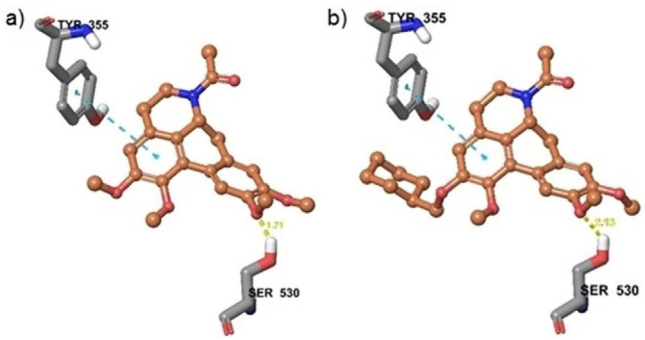


Figure 4. Docking results for compounds a) **27q** and b) **27a** having total docking scores of 7.4851 and 5.9304, respectively.

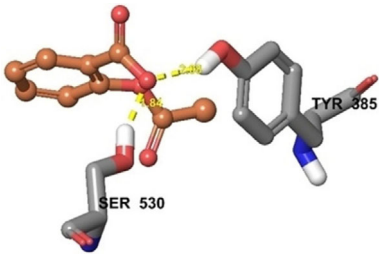


Figure 5. Docking results for acetylsalicylic acid showing a docking score of 4.9713 and the formation of two H-bonds to polar, uncharged, and nucleophilic Ser-530 (1.84 Å) and the OH group of Tyr-355 (2.08 Å).

In the docking pose, the binding-site residues within a radius of 3 Å from the bound compound were aliphatic, hydrophobic Ile-517, Ile-523, Leu-352, Leu-359, Leu-531, Val-349, and Ala-527; aromatic, hydrophobic Tyr-348, Tyr-355, Tyr-385, Phe-518, and Trp-387; and polar, uncharged, nucleophilic Ser-353 and Ser-530. Furthermore, the binding interaction and binding affinities of compounds **27q** and **27a** were compared with that of acetylsalicylic acid.

The docking results for acetylsalicylic acid showed a comparatively lower binding affinity indicated by a docking score of 4.9713 and formed two H-bonds to polar, uncharged, and nucleophilic Ser-530 (1.84 Å) and the OH group of Tyr-355 (2.08 Å) (Figure 5). In the docking pose, the binding-site residues within a radius of 3 Å from the bound acetylsalicylic acid were aliphatic, hydrophobic Leu-352, Leu-384, Val-349, Gly-526, and Ala-527; aromatic, hydrophobic Tyr-348, Tyr-385, Phe-381, and Trp-387; and polar, uncharged, nucleophilic Ser-530. Chemical analysis of the binding of the amino acid residues for compounds **27a** and **27q** and acetylsalicylic acid revealed that these compounds bind to hydrophobic and hydrophilic residues, and the hydrophobic residues stabilize in the binding pocket and the H-bond network is established by hydrophilic residues.

Furthermore, comparison of the binding amino acid residues revealed that the majority of the interacting residues belonged to hydrophobic amino acids. Thus, the presence of hydrophobic residues imparts greater stability and inhibition activity than the standard reference (i.e., acetylsalicylic acid). The docking results allowed us to infer that synthesized aporphine analogues **27a** and **27q** showed better antiplatelet activity owing to the fact that it had greater binding affinity than acetylsalicylic acid.

Following the redocking approach, the synthesized aporphine analogues showing good activity (i.e., **27b**, **27f**, **27h**, **27j**, **27l**, and **27n**) were selected for docking into the binding site of the antioxidant target protein (PDB ID: 3MNG), and the binding affinities were compared with that of ascorbic acid as a standard drug.

The docking results for selected active compounds revealed good binding affinity. Among the selected compounds, **27j** displayed the highest binding affinity in terms of docking score (5.1878). Compound **27j** forms two H-bonds to Arg-127 (2.62 and 2.12 Å) and Thr-147 (1.98 Å) (Figure 6a). In the docking pose, the binding-site residues within a radius of 3 Å from the bound compound were cyclic, hydrophobic Pro-40 and Pro-45; aliphatic, hydrophobic Gly-46, Leu-116, Leu-149, and Ile-119; aromatic, hydrophobic Phe-120; basic, polar, and positively charged Arg-127; and polar, uncharged, and nucleophilic Thr-147.

Similarly, compounds **27n**, **27l**, **27f**, **27h**, and **27b** showed good binding affinity in terms of docking scores of 4.7335, 4.6290, 4.4967, 3.9514, and 2.9735, respectively (Figures 6b–d and 7). For all of the compounds, the common binding amino acid residues within a radius of 3 Å from the bound compounds were cyclic, hydrophobic Pro-45; aliphatic, hydrophobic Gly-46 and Leu-149; polar, positively charged Lys-49 and Arg-127; and polar uncharged, nucleophilic Thr-147. These compounds showed multiple H-bonds to binding amino acid residues.

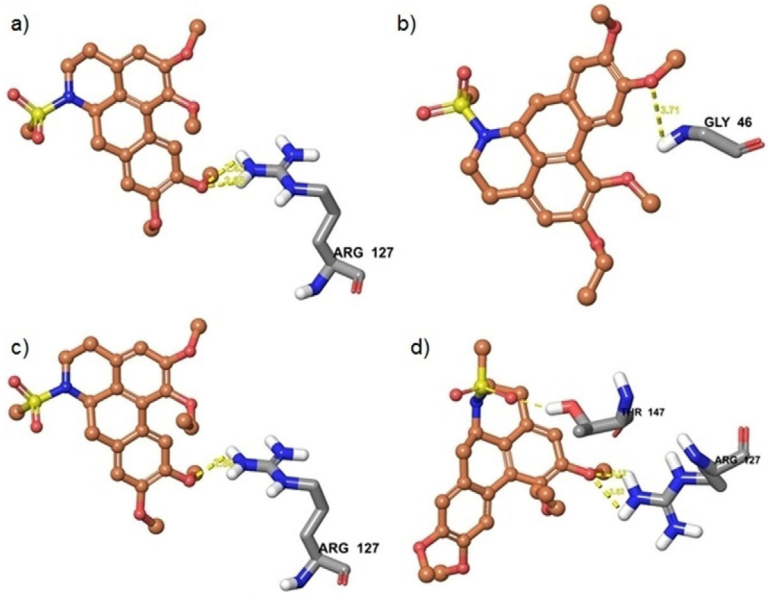


Figure 6. Docking scores of a) **27 j**, b) **27 n**, c) **27 l**, and d) **27 f** revealed good binding affinity in terms of docking scores of 5.1878, 4.7335, 4.6290, and 4.4967, respectively.

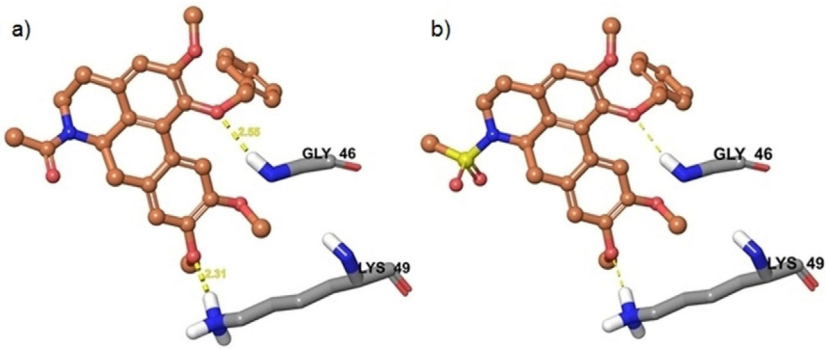


Figure 7. Docking scores of a) **27 h** and b) **27 b** revealed binding affinity in terms of docking scores 3.9514 and 2.9735, respectively.

Furthermore, the binding interaction of ascorbic acid (docking score 4.2924) was explored, and we found similar binding-interaction amino acid residues within a radius of 3 Å that comprised cyclic, hydrophobic Pro-40 and Pro-45; aliphatic, hydrophobic Gly-46 and Leu-116; polar, uncharged, and nucleophilic Thr-44, Thr-147, and Cys-47; and basic, polar, and positively charged Arg-127 (Figure 8). Moreover, after analyzing the chemical nature of the binding-site amino acid residues, it was revealed that these compounds have a propensity to form hydrophobic interactions and multiple H-bonds with the hydrophilic residues of the target protein. Thus, comparison of the binding affinities of the aporphine analogues with that of ascorbic acid showed that these compounds have better antioxidant activity.

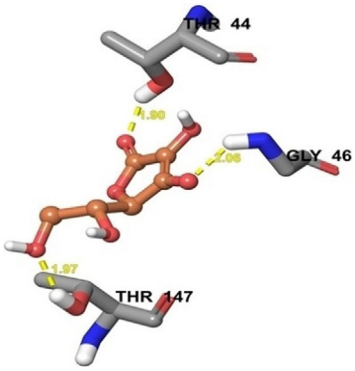


Figure 8. Binding interactions of the standard drug ascorbic acid (docking score = 4.2924).

Conclusions

We herein disclosed the identification of novel aporphine analogues as potent antiplatelet and antioxidant agents by structural manipulation on ring A (at the C1/C2 positions) and the N6 position of the aporphine skeleton. The SAR study suggested that alkoxy substituents at the C1 and C2 positions of ring A and the N6 substituent could be modified to develop potent antiplatelet and antioxidant agents. In arachidonic acid

induced platelet aggregation inhibitory activity, aporphine analogues 1-[1,2,9,10-tetramethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]-quinolin-6(5*H*)-yl]ethanone (**27 a**) and 1-[2-(benzyloxy)-1,9,10-trimethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]quinolin-6(5*H*)-yl]-ethanone (**27 q**) (having an acetyl group at the N6 position, a OCH_3 or OCH_2Ph substituent at C1, and a OCH_3 substituent at the C2 position of ring A) were the most active compounds of the series. Moreover, in a preliminary 2,2-diphenyl-1-picrylhydrazyl (DPPH) free-radical antioxidant activity assay, aporphine analogues 1,2,9,10-tetramethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (**27 b**), 2-ethoxy-1,9,10-trimethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo-[*de*,*g*]quinoline (**27 f**), 1-ethoxy-2,9,10-trimethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (**27 h**), 2,9,10-trimethoxy-6-(methylsulfonyl)-1-propoxy-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (**27 j**), and 1-(benzyloxy)-2,9,10-trimethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (**27 n**) (methylsulfonyl substituent at the N6 position with a OCH_3 or OC_2H_5 substituent at C1 and a OCH_3, OC_3H_7, or OCH_2Ph substituent at C2 of ring A) were the most active compounds of the series. Our results showed that the substituent at the N6 position played a very important role in antiplatelet and antioxidant activity. Interestingly, it was possible, through structural modifications, to synthesize potent aporphines showing both activities, as displayed by aporphine analogue 1-[1-(benzyloxy)-2,9,10-trimethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]quinolin-6(5*H*)-yl]ethanone (**27 l**) in our study. In addition, to check the binding interaction and docking score, in silico molecular docking studies were also performed for the reference standard and the promising active analogues for antiplatelet and antioxidant activities. Moreover, the SAR effects related to modification at C1/C2 of ring A and the N6 position of ring B provided the necessary aspects for any future undertaking to understand the role of different functional groups at specific positions in active analogues for their therapeutic potential. Succinctly, these lead compounds are considered worthy of further structural optimization and development as potential antiplatelet and antioxidant agents.

Experimental Section

General methods

All glass apparatus were oven dried prior to use. Melting points were taken in open capillaries with a Complab melting point apparatus. Infrared spectra were recorded with a PerkinElmer FTIR Spectrum 2 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with an ECS 400 MHz (JEOL) NMR spectrometer by using $CDCl_3$ and CD_3SOCD_3 as solvents and tetramethylsilane as an internal reference. Electrospray ionization mass spectrometry (ESI-MS) and HRMS were recorded with an Xevo G2-S QToF (Waters, USA) spectrometer. A microwave reactor (CEM Discover) was used for the reactions. Column chromatography was performed over Merck silica gel (particle size: 60–120 mesh and 230–400 mesh) procured from Qualigens (India) and flash silica gel (particle size: 230–400 mesh). All chemicals and reagents were obtained from Sigma–Aldrich (USA), Merck (India), or Spectrochem (India) and were used without further purification.

Synthesis

General procedure for the synthesis of 2-(2-bromophenyl)-*N*-phenethylacetamide analogues 21 a–f

A solution of 2-(2-bromo-4,5-dimethoxyphenyl)acetic acid (**20**; 10.0 mmol, 1 equiv) and 1,10-carbonyldiimidazole (10.0 mmol, 1 equiv) in anhydrous THF (25 mL) was stirred at room temperature for 1 h. The mixture was then cooled at 0 °C and phenethylamine analogue **19 a–f** (10.0 mmol, 1 equiv) was added, The mixture was stirred at 0 °C for 4 h and then at room temperature overnight. The mixture was concentrated under reduced pressure, and the obtained residue was dissolved in EtOAc (20 mL) and washed sequentially with 1 N HCl (15 mL), water (2×25 mL), satd. $NaHCO_3$ solution (2×15 mL), and brine (30 mL). The organic layer was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. The resultant crude products were purified by recrystallization (EtOAc/hexane 20:80, *v*/*v*) or by flash column chromatography (silica gel, hexane/EtOAc 9:1), which furnished the 2-(2-bromophenyl)-*N*-phenethylacetamide analogue (2–84% yield).

2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-(3,4-dimethoxyphenethyl)-acetamide (21 a): White solid (81%); R_f ($MeOH/CH_2Cl_2$ 5:95) = 0.52; purification by flash column chromatography (deactivated silica gel, $MeOH/CH_2Cl_2$ 2:98); mp: 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (s, 1H), 6.98 (d, J = 8.4 Hz 1H), 6.91 (d, J = 1.6 Hz, 1H), 6.85 (dd, J = 2.0, 10.4 Hz, 1H), 5.75 (s, 1H), 4.15–4.10 (m, 12H), 3.86 (s, 2H), 3.74 (q, J = 6.8 Hz, 2H), 2.98 ppm (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 149.0, 148.8, 147.7, 131.1, 126.6, 120.7, 115.6, 114.8, 113.8, 111.8, 111.2, 56.3, 56.2, 56.2, 55.9, 43.7, 40.8, 35.0 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 3414, 2935, 1633, 1549, 1463, 1384, 1244, 1028 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{24}BrNO_5$: 439.0838 $[M+2]^+$; found: 439.0832.

2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-(3-methoxy-4-propoxyphenethyl)acetamide (21 b): White solid (72%); R_f ($MeOH/CH_2Cl_2$ 5:95) = 0.60; purification by flash column chromatography (deactivated silica gel, $MeOH/CH_2Cl_2$ 2.5:97.5); mp: 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (s, 1H), 6.76 (s, 1H), 6.72 (d, J = 8.0 Hz 1H), 6.63–6.62 (m, 1H), 6.56–6.54 (m, 1H), 5.46 (s, 1H), 3.95–3.90 (m, 2H), 3.87–3.77 (m, 9H), 3.58 (s, 2H), 3.45 (q, J = 6.8 Hz 2H), 2.68 (t, J = 6.8 Hz, 2H), 1.84 (q, J = 7.6 Hz, 2H), 1.02 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 149.6, 149.1, 147.3, 131.1, 126.7, 120.7, 115.6, 114.9, 113.8, 113.1, 112.4, 70.7, 56.3, 56.2, 56.1, 43.8, 40.9, 35.1, 22.6, 10.6 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 3300, 2930, 1638, 1511, 1465, 1338, 1260, 1027 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{28}BrNO_5$: 467.1151 $[M+2]^+$; found: 467.1156.

***N*-[4-(Benzyloxy)-3-methoxyphenethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (21 c)**: White solid (78%); R_f ($MeOH/CH_2Cl_2$ 4:96) = 0.55; purification by flash column chromatography (deactivated silica gel, $MeOH/CH_2Cl_2$ 2:98); mp: 125–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.42 (m, 2H), 7.38–7.27 (m, 2H), 6.96 (s, 1H), 6.82- 6.72 (m, 3H), 6.65(s, 1H), 6.52–6.49 (m, 1H), 5.45 (s, 1H), 5.12 (s, 2H), 3.87- 3.82 (m, 9H), 3.57 (s, 2H) 3.48–3.42 (m, 2H) 2.74–2.67 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 149.8, 149.0, 148.2, 146.9, 137.4, 131.8, 128.7, 127.9, 127.4, 126.7, 120.7, 115.6, 114.9, 114.2, 113.8, 112.4, 71.2, 56.3, 56.2, 56.0, 43.8, 40.8, 35.1 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 3387, 2900, 1635, 1510, 1463, 1384, 1265, 1030 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{28}BrNO_5$: 515.1151 $[M+2]^+$; found: 515.1155.

2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-(3-ethoxy-4-methoxyphenethyl)acetamide (21 d): White solid (84%); R_f ($MeOH/CH_2Cl_2$ 5:95) = 0.55; purification by flash column chromatography (deactivated silica gel, $MeOH/CH_2Cl_2$ 3:97); mp: 119–121 °C; ^{1}H NMR (400 MHz,

$CDCl_3$): $\delta = 6.97$(s, 1H), 6.70 (d, $J = 8.0$ Hz 1H), 6.64–6.63 (m, 1H), 6.57–6.54 (m, 1H), 5.45 (s, 1H), 4.03 (q, $J = 7.2$ Hz 2H), 3.86–3.82 (m, 9H), 3.57 (s, 1H), 3.44 (q, $J = 6.4$ Hz, 2H), 2.67 (t, $J = 6.8$ Hz, 2H), 1.44 ppm (t, $J = 7.2$ Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.9$, 149.0, 148.8, 148.5, 148.0, 131.1, 126.7, 120.7, 115.6, 114.9, 113.3, 111.6, 64.4, 56.3, 56.2, 56.1, 43.8, 40.9, 35.1, 14.9 ppm; FTIR (KBr): $\tilde{\nu}_{max} = 3300$, 2930, 1638, 1511, 1465, 1338, 1260, 1027 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{21}H_{26}BrNO_5$: 453.0994 $[M+2]^+$; found: 453.0998.

***N*-[3-(Benzyloxy)-4-methoxyphenethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (21e)**: White solid (79%); R_f (MeOH/CH_2Cl_2 5:95) = 0.60; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 3:97); mp: 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.44$–7.42 (m, 2H), 7.35 (t, $J = 14.8$ Hz, 2H), 7.31–7.29 (m, 1H), 6.97 (s, 1H), 6.74–6.67 (m, 3H), 6.60–6.57 (m, 1H), 5.41 (s, 1H), 4.15–4.10 (m, 12H), 3.86 (s, 2H), 3.74 (q, $J = 6.8$ Hz, 2H), 2.98 ppm (t, $J = 6.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.9$, 149.0, 148.8, 148.5, 148.3, 137.2, 131.0, 128.7, 127.9, 127.5, 126.7, 121.4, 115.6, 114.9, 114.7, 113.8, 111.9, 71.1, 56.3, 56.2, 56.1, 43.9, 43.8, 40.8, 34.9 ppm; FTIR (KBr): $\tilde{\nu}_{max} = 3387$, 2930, 1635, 1513, 1463, 1384, 1260, 1029 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{26}H_{28}BrNO_5$: 515.1151 $[M+2]^+$; found: 515.1158.

2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-(4-ethoxy-3-methoxyphenethyl)acetamide (21f): White solid (75%); R_f (MeOH/CH_2Cl_2 5:95) = 0.55; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 2:98); mp: 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.97$ (s, 1H), 6.76 (s, 1H), 6.71 (d, $J = 7.6$ Hz 1H), 6.63–6.62 (m, 1H), 6.56–6.53 (m, 1H), 5.46 (s, 1H), 4.08- 4.03 (m, 2H), 3.90–3.81 (m, 9H), 3.57 (s, 2H), 3.45 (q, $J = 6.8$ Hz, 2H), 2.68 (t, $J = 6.8$ Hz, 2H), 1.44 ppm (t, $J = 7.2$ Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.9$, 149.4, 149.0, 148.8, 147.0, 131.1, 126.7, 120.7, 115.6, 114.9, 113.8, 112.8, 112.1, 64.4, 56.3, 56.2, 55.9, 43.8, 40.9, 35.1, 14.9 ppm; FTIR (KBr): $\tilde{\nu}_{max} = 3297$, 2930, 1636, 1551, 1464, 1337, 1213, 1164 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{21}H_{26}BrNO_5$: 453.0994 $[M+2]^+$; found: 453.0999.

General procedure for the synthesis of 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline analogues 23a–f

Solid PCl_5 (10.0 mmol, 2 equiv) was added in portions over a 10 min period to a stirred ice-cooled solution of 2-(2-bromophenyl)-*N*-phenethylacetamide analogue **21a–f** (5.00 mmol, 1 equiv) in dry CH_2Cl_2 (20 mL). The mixture was stirred at 0 °C for 1 h and then at room temperature for 12 h. The mixture was poured onto a saturated aqueous solution of $NaHCO_3$ (30 mL) and was stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL), and the combined organic phase was sequentially washed with saturated $NaHCO_3$ solution (2×20 mL) and brine (30 mL), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. Crude imine **22a–f** was immediately used in the next step.

Sodium borohydride (5.20 mmol, 1.3 equiv) was added slowly in three portions over a 10 min period to a stirred ice-cooled solution of crude imine **22a–f** (4.00 mmol, 1.0 equiv) in MeOH (15 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. The mixture was cooled to 0 °C, diluted with water (5 mL), and extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with brine (25 mL), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure to afford the crude product. Crude oily amine **23a–f** was immediately used in the next step without further purification (*CAUTION: compounds **23a–f** cannot be stored for a long time, as they decompose if stored for more than 24 h*).

General procedure for the synthesis of *N*-Boc-protected 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline analogues 24a–f

iPr_2NEt (6.00 mmol, 2 equiv), 4-(dimethylamino)pyridine (DMAP) (0.01 g), and Boc_2O (3.6 mmol, 1.2 equiv) were added to a stirred solution of crude oily amine **23a–f** (3.00 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at room temperature, and the resulting mixture was stirred for 18 h. The mixture was then quenched with aqueous NH_4Cl (2 mL), extracted with CH_2Cl_2 (3×50 mL) and water (20 mL), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The resultant crude product was purified by flash column chromatography (deactivated 100–200 mesh silica gel, 100% EtOAc), which furnished Boc-protected 1-(2-bromo-3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline analogue **24a–f** as a white crystalline solid in good yield (70–83%).

***tert*-Butyl 1-(2-bromo-4, 5-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (24a)**: White solid (76%); R_f (MeOH/CH_2Cl_2 5:95) = 0.55; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 3:97); mp: 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): $\delta = 7.03$ and 6.96 (m, 1H, both rotamers), 6.73 and 6.64 (m, 1H, both rotamers), 6.61 and 6.57 (m, 1H, both rotamers), 6.51–6.47 (m, 1H, both rotamers), 5.39–5.35 and 5.25- 5.22 (m, 1H, both rotamers), 4.36–4.31 (m, 1H, both rotamers), 3.90–3.73 (m, 12H, both rotamers), 3.38–3.18 (m, 2H, both rotamers), 3.05–2.85 (m, 2H, both rotamers), 2.65–2.61 (m, 1H, both rotamers), 1.37 and 1.16 ppm (m, 2+7 = 9H, both rotamers); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamers): $\delta = 154.3$, 148.6, 148.4, 147.9, 147.5, 130.4, 128.9, 126.7, 115.5, 114.4, 111.5, 110.1, 79.5, 56.4, 56.3, 56.0, 54.4, 42.2, 36.6, 28.5, 28.3, 28.1 ppm; FTIR (KBr): $\tilde{\nu}_{max} = 3418$, 1690, 1468, 1361, 1253, 1169, 1111 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{25}H_{32}BrNO_6$: 523.1413 $[M+2]^+$; found: 523.1418.

***tert*-Butyl 1-(2-bromo-4,5-dimethoxybenzyl)-6-methoxy-7-propoxy-3, 4-dihydroisoquinoline-2(1*H*)-carboxylate (24b)**: White solid (70%); R_f (MeOH/CH_2Cl_2 5:95) = 0.65; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 2:98); mp: 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): $\delta = 7.03$ and 6.96 (m, 1H, both rotamers), 6.75 (m, 1H, both rotamers), 6.63 and 6.61 (m, 1H, both rotamers), 6.57 and 6.51 (m, 1H, both rotamers), 5.36–5.34 and 5.26–5.16 (m, 1H, both rotamers), 4.34–4.30 (m, 1H, both rotamers), 3.96–3.90 (m, 1H, both rotamers), 3.84–3.78(m, 9H, both rotamers), 3.29–3.12 (m, 2H, both rotamers), 3.02–2.49 (m, 3H, both rotamers), 2.02–1.53 (m, 3H, both rotamers), 1.36 and 1.15 (m, 7+2 = 9H, both rotamers), 1.06–0.94 ppm (m, 3H, both rotamers); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): $\delta = 154.3$, 148.5, 148.4, 148.0, 147.0, 130.4, 128.9, 126.7, 115.5, 115.2, 114.4, 111.9, 111.9, 79.5, 70.9, 56.4, 56.3, 56.2, 54.4, 42.3, 36.6, 28.5, 28.3, 28.1 ppm; FTIR (KBr): $\tilde{\nu}_{max} = 3416$, 1685, 1512, 1415, 1385, 1260, 1164, 1098 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{27}H_{36}BrNO_6$: 551.1726 $[M+2]^+$; found: 551.1721.

***tert*-Butyl 7-(benzyloxy)-1-(2-bromo-4,5-dimethoxybenzyl)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (24c)**: White solid (83%); R_f (MeOH/CH_2Cl_2 5:95) = 0.60; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 3:97); mp: 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) 7.46–7.27 (m, 5H, both rotamers), 7.02 and 6.96 (m, 1H, both rotamers), 6.77 (s, 1H, major rotamer), 6.63–6.47(m, 2H, both rotamers), 5.31–4.95 (m, 3H, both rotamers), 4.36–4.32 (m, 1H, both

rotamers), 3.91–3.76 (m, 9H, both rotamers), 3.35–3.13 and 3.06–3.01 (m, 2H, both rotamers), 2.92- 2.71 and 2.63–2.50 (m, 3H, both rotamers), 1.36 and 1.13 ppm (m, 7+2=9H, both rotamers); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ=154.3, 148.6, 148.5, 148.4, 146.6, 137.2, 130.5, 128.7, 127.9, 127.4, 127.4, 115.4, 115.0, 114.3, 113.1, 111.9, 79.5, 71.5, 56.4, 56.2, 54.2, 42.2, 38.9, 36.4, 28.5, 28.1 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=3418, 1689, 1513, 1408, 1387, 1252, 1163, 1104 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{31}H_{36}BrNO_6$: 599.1726 $[M+2]^+$; found: 599.1722.

***tert*-Butyl 1-(2-bromo-4,5-dimethoxybenzyl)-6-ethoxy-7-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (24 d)**: White solid (72%); R_f (MeOH/CH_2Cl_2 5:95)=0.65; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 2:98); mp: 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ=7.03 and 6.96 (m, 1H, both rotamers), 6.73 and 6.65 (m, 1H, both rotamers), 6.61 and 6.57 (m, 1H, both rotamers), 6.52–6.47 (m, 1H, both rotamers), 5.38–5.35 and 5.25- 5.22 (m, 1H, both rotamers), 4.35–4.31 (m, 1H, both rotamers), 4.12–4.01 (m, 2H, both rotamers), 3.86–3.72 (m, 9H, both rotamers), 3.39–3.32 and 3.29–3.18 (m, 2H, both rotamers), 3.05–3.00 and 2.95- 2.84 (m, 2H, both rotamers), 2.80–2.72 and 2.64–2.53 (m, 1H, both rotamers), 1.47–1.43 (m, 3H, both rotamers), 1.38 and 1.17 ppm (m, 2+7=9H, both rotamers); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ=154.3, 148.6, 148.4, 147.8, 147.3, 130.5, 128.9, 126.7, 115.5, 115.1, 114.4, 112.9, 110.4, 79.5, 64.5 56.5, 56.3, 56.2, 42.3, 36.6, 28.5, 28.3, 28.1, 14.9 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=3415, 1687, 1503, 1384, 1033 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{26}H_{34}BrNO_6$: 537.1570 $[M+2]^+$; found: 537.1576.

***tert*-Butyl 6-(benzyloxy)-1-(2-bromo-4,5-dimethoxybenzyl)-7-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (24 e)**: White solid (74%); R_f (MeOH/CH_2Cl_2 5:95)=0.60; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 2.5:97.5); mp: 149–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ=7.45–7.28 (m, 5H, both rotamers), 7.04 and 6.97 (m, 1H, both rotamers), 6.76 (s, 1H, major rotamer), 6.65–6.61 (m, 1H, both rotamers), 6.51–6.50 (m, 1H, both rotamers), 5.39–5.35 and 5.26–5.22 (m, 1H, both rotamers), 5.12–5.11 (m, 2H, both rotamers), 4.33–4.29 (m, 1H, both rotamers), 3.86–3.74 (m, 9H, both rotamers), 3.37–3.18 (m, 2H, both rotamers), 3.05–3.30 and 2.95–2.80 (m, 2H, both rotamers), 2.60–2.51 (m, 1H, both rotamers), 1.37 and 1.17 ppm (m, 7+2=9H, both rotamers); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ=154.3, 148.6, 148.4, 148.2, 147.2, 137.2, 130.4, 129.5, 128.7, 127.9, 127.4, 126.7, 115.5, 115.0, 114.4, 114.1, 110.8, 79.5, 71.1, 56.5, 56.3, 56.1, 54.5, 42.3, 36.6, 28.5, 28.1 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=3418, 2929, 1687, 1512, 1461, 1252, 1163 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{31}H_{36}BrNO_6$: 599.1726 $[M+]^+$; found: 599.1729.

***tert*-Butyl 1-(2-bromo-4,5-dimethoxybenzyl)-7-ethoxy-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (24 f)**: White solid (78%); R_f (MeOH/CH_2Cl_2 5:95)=0.60; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 3:97); mp: 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ=7.03 and 6.96 (m, 1H, both rotamers), 6.77–6.51 (m, 3H, both rotamers), 5.36–5.21 (m, 1H, both rotamers), 4.36–4.31 and 4.09–4.03 (m, 1H, both rotamers), 3.91–3.79 (m, 11H, both rotamers), 3.28–3.17 (m, 2H, both rotamers), 3.02–2.54 (m, 2H, both rotamers), 1.48–1.32 (m, 6H, both rotamers), 1.24–1.16 ppm (m, 6H, major rotamer); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ=154.3, 148.6, 148.4, 148.3, 146.8, 130.5, 128.9, 126.8, 115.5, 115.0, 114.4, 111.7, 111.7, 79.5, 64.7, 56.4, 56.3, 56.1, 54.4, 42.3, 36.6, 28.5, 28.3, 28.1 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=3419, 1687, 1510, 1417, 1383, 1257, 1162, 1097 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{26}H_{34}BrNO_6$: 537.1570 $[M+2]^+$; found: 537.1578.

General procedure for the synthesis of biaryl-coupled N-protected 1,2,9,10-tetramethoxy-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline analogues 25 a–f

$Pd(OAc)_2$ (0.02 mmol, 20 mol%), ligand di-*tert*-butyl(methyl)phosphonium tetrafluoroborate (0.04 mmol, 40 mol%), K_2CO_3 (0.3 mmol, 3 equiv), and pivalic acid (0.04 mmol, 40 mol%) were added to a solution of compound **24 a–f** (0.10 mmol, 1 equiv) in DMSO (1.0 mL) in a microwave vial by purging with nitrogen, and the mixture was irradiated in a microwave reactor in a sealed vial for 5 min at 135 °C. After cooling to room temperature, the mixture was loaded onto deactivated silica gel column (100–200 mesh) and eluted with EtOAc/hexanes (35:65, *v/v*) to afford desired N-protected 1,2,9,10-tetramethoxy-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline analogue **25 a–f** as a white solid in excellent yields (up to 73–92%).

***tert*-Butyl 1,2,9,10-tetramethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]-quinoline-6(5*H*)-carboxylate (25 a)**: White solid (80%); R_f (EtOAc/hexane 40:60)=0.65; purification by flash column chromatography (deactivated silica gel, hexane/EtOAc 7:3); mp: 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.15 (s, 1H), 6.76 (s, 1H), 6.63 (s, 1H), 4.67–4.39 (m, 5H), 3.92–3.89 (m, 9H), 3.65 (s, 3H), 2.97–2.74 (m, 4H), 2.65–2.62 (m, 1H), 1.49 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.7, 152.0, 148.3, 147.4, 144.7, 130.2, 130.0, 128.2, 127.7, 125.9, 125.7, 124.2, 124.1, 111.7,110.9, 110.6,79.9, 60.1, 55.9, 55.9, 51.9, 51.8, 38.9, 34.8, 30.6, 29.7 28.6 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=3416, 2941, 1632, 1518, 1465, 1328, 1253, 1199, 1023 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{25}H_{31}NO_6$: 442.2224 $[M+H]^+$; found: 442.2229.

***tert*-Butyl 2,9,10-trimethoxy-1-propoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]quinoline-6(5*H*)-carboxylate (25 b)**: White solid (84%); R_f (EtOAc/hexane 40:60)=0.60; purification by flash column chromatography (deactivated silica gel, hexane/EtOAc 7:3); mp: 95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.15 (s, 1H), 6.75 (s, 1H), 6.61 (s, 1H), 4.61 (s, 1H), 4.38(s, 1H), 3.91–3.85 (m, 9H), 3.81–3.75 (m, 2H), 3.55 (q, *J*=8.4 Hz, 1H), 2.90–2.61 (m, 4H), 1.76–1.69 (m, 2H), 1.48–1.46 (m, 9H), 0.92 ppm (t, *J*=7.6 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.8, 152.0, 148.2, 147.2, 144.0, 130.1, 129.9, 128.0, 125.9, 124.5, 112.1, 110.9, 110.6, 79.9, 74.9, 55.9, 55.9, 55.9, 52.0, 38.9, 35.2, 30.5, 28.7, 23.8, 10.5 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=3417, 2933, 1691, 1512, 1462, 1391, 1247, 1045 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{27}H_{35}NO_6$: 470.2537 $[M+H]^+$; found: 470.2532.

***tert*-Butyl 1-(benzyloxy)-2,9,10-trimethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]quinoline-6(5*H*)-carboxylate (25 c)**: White solid (88%); R_f (EtOAc/hexane 40:60)=0.60; purification by flash column chromatography (deactivated silica gel, hexane/EtOAc 7.5:2.5); mp: 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07 (s, 1H), 7.39–7.29 (m, 5H), 6.76 (s, 1H), 6.66 (s, 1H), 4.92 (d, *J*=8.0 Hz, 1H), 4.66 (d, *J*=12.0 Hz, 1H), 4.52 (d, *J*=12.0 Hz, 1H), 4.41 (d, *J*=8.0 Hz, 1H), 3.92 (s, 6H), 3.51 (s, 3H), 2.98–2.64 (m, 5H), 1.49 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.8, 152.2, 148.2, 147.2, 143.6, 137.4, 129.9, 128.8, 128.4, 128.2, 112.1, 110.9, 79.9, 74.7, 56.1, 55.9, 55.5, 51.9, 38.8, 35.2, 30.6, 28.7 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=3413, 2972, 1686, 1595, 1466, 1391, 1250, 1112 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{31}H_{35}NO_6$: 518.2537 $[M+H]^+$; found: 518.2533.

***tert*-Butyl 2-ethoxy-1,9,10-trimethoxy-6*a*,7-dihydro-4*H*-dibenzo-[*de*,*g*]quinoline-6(5*H*)-carboxylate (25 d)**: White solid; 90%); R_f (EtOAc/hexane 40:60)=0.65; purification by flash column chromatography (deactivated silica gel, hexane/EtOAc 7:3); mp: 101–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.17 (s, 1H), 6.76 (s, 1H), 6.62 (s, 1H), 4.68–4.65 (m, 1H), 4.38 (s, 1H), 4.12–4.07 (m, 2H), 3.90 (d, *J*=7.2 Hz, 6H), 3.67 (s, 3H), 2.97–2.60 (m, 5H), 1.51–1.46 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.8, 151.3, 148.3, 147.4,

144.9, 130.1, 127.8, 125.8, 124.4, 111.8, 111.6, 110.9, 79.9, 64.2, 60.0, 56.0, 55.9, 51.9, 38.8, 34.9, 30.5, 28.6, 15.5 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 3417, 2930, 1681, 1514, 1412, 1380, 1250, 1105 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{26}H_{33}NO_6$: 456.2381 $[M+H]^+$; found: 456.2386.

***tert*-Butyl 2-(benzyloxy)-1,9,10-trimethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]quinoline-6(5*H*)-carboxylate (25 e)**: White solid (73%); R_f (EtOAc/hexane 40:60) = 0.60; purification by flash column chromatography (deactivated silica gel, hexane/EtOAc 7.5:3.5); mp: 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1H), 7.46–7.37 (m, 5H), 6.75 (s, 1H), 6.68 (s, 1H), 5.13 (q, *J* = 12.0 Hz, 2H), 4.67 (s, 1H), 4.37 (s, 1H), 3.91 (d, *J* = 2.4 Hz, 6H), 3.69 (s, 3H), 2.92–2.74 (m, 4H), 2.59 (d, *J* = 15.2 Hz, 1H), 1.48 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 151.0, 148.1, 147.2, 145.0, 136.9, 129.9, 128.5, 127.9, 127.8, 127.2, 126.2, 124.2, 112.2, 111.6, 110.8, 79.8, 70.7, 60.0, 55.9, 55.7, 51.8, 38.4, 34.8, 30.3, 28.5 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 3416, 2930, 1690, 1513, 1460, 1380, 1252, 1027 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{31}H_{35}NO_6$: 518.2537 $[M+H]^+$; found: 518.2532.

***tert*-Butyl 1-ethoxy-2,9,10-trimethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]quinoline-6(5*H*)-carboxylate (25 f)**: White solid (79%); R_f (EtOAc/hexane 40:60) = 0.65; purification by flash column chromatography (deactivated silica gel, hexane/EtOAc 7:3); mp: 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (s, 1H), 6.75 (s, 1H), 6.61 (s, 1H), 4.63 (d, *J* = 12.4 Hz 1H), 4.39 (d, *J* = 8.0 Hz, 1H), 3.94–3.91 (m, 6H), 3.87 (s, 3H), 3.68–3.60 (m, 1H), 2.96–2.73 (m, 4H), 2.62 (d, *J* = 14.8 Hz, 1H), 1.48 (s, 9H), 1.31 ppm (t, *J* = 7.2 Hz 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 152.1, 148.2, 147.2, 143.8, 130.1, 130.1, 128.1, 125.9, 124.5, 111.9, 110.9, 110.9, 110.5, 79.9, 68.6, 55.9, 55.9, 52.0, 38.7, 35.0, 30.5, 29.8, 28.6, 16.0 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 3417, 2934, 1685, 1515, 1463, 1391, 1252, 1018 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{26}H_{33}NO_6$: 456.2308 $[M+H]^+$; found: 456.2303.

General procedure for the synthesis of 1,2,9,10-tetramethoxy-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline analogues 26 a–f

Anhydrous $ZnBr_2$ (4.00 mmol, 4 equiv) was added to a solution of compound **25 a–f** (1.00 mmol, 1 equiv) in dry CH_2Cl_2 (10 mL) under a nitrogen atmosphere, and the mixture was stirred at room temperature for 6 h. The mixture was then quenched with a solution of saturated $NaHCO_3$ (10 mL) and was extracted with CH_2Cl_2 (3× 50 mL). The combined organic layer was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure to afford crude amine **26 a–f**, which was immediately used in the next step without any further purification. (*CAUTION: compound was found to be unstable for long-term storage*).

General procedure for the synthesis of *N*-acetyl/benzoyl/methylsulfonyl/*m*-tolylsulfonyl-protected 1,2,9,10-tetramethoxy-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline analogues 27 a–o and 27 q–s

Triethylamine (0.50 mmol, 2.5 equiv) was added to a solution of crude amine **26 a–f** (0.20 mmol, 1 equiv) in anhydrous CH_2Cl_2 (20 mL), followed by acetyl chloride (0.24 mmol, 1.2 equiv), methanesulfonyl chloride (0.24 mmol, 1.2 equiv), *p*-toluenesulfonyl chloride (0.22 mmol, 1.1 equiv), or benzoyl chloride (0.22 mmol, 1.1 equiv) at room temperature, and the mixture was stirred for 8 h under a N_2 atmosphere. The mixture was quenched with $NaHCO_3$ (5% aqueous solution, 10 mL) and extracted with CH_2Cl_2 (3× 50 mL). The combined organic phase was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (MeOH/CH_2Cl_2 1:99, *v/v*), which furnished **27 a–o** or **27 q–s** (69–93%) as a white solid.

1-[1,2,9,10-Tetramethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]quinolin-6(5*H*)-yl]ethanone (27 a): White solid (73%); R_f (MeOH/CH_2Cl_2 5:95) = 0.55; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 3:97); mp: 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$, both rotamers): δ = 8.17–8.14 (m, 1H), 6.78–6.76 (m, 1H), 6.65–6.62 (m, 1H), 5.08–4.94 (m, 1H), 4.00–3.83 (m, 10H), 3.65 (s, 3H), 3.33–3.27 (m, 1H), 3.08–2.63 (m, 5H), 2.21–2.18 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 169.2, 152.1, 148.4, 147.5, 145.0, 130.6, 129.9, 129.2, 128.0, 125.9, 124.0, 111.7, 110.9, 60.1, 56.0, 54.2, 50.8, 42.2, 36.2, 33.6, 30.9, 22.8 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 2943, 2847, 1607, 1575, 1418, 1256, 1034 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{22}H_{25}NO_5$: 384.1805 $[M+H]^+$; found: 384.1801.

1,2,9,10-Tetramethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 b): White solid (93%); R_f (MeOH/CH_2Cl_2 5:95) = 0.65; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 3:97); mp: 258–260 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1H), 6.78 (s, 1H), 6.63 (s, 1H), 4.49 (t, *J* = 9.6 Hz, 1H), 4.12–4.09 (m, 1H), 3.92–3.89 (m, 9H), 3.65–3.64 (m, 3H), 3.30–3.23 (m, 1H), 2.99 (d, *J* = 10 Hz, 2H), 2.94–2.86 (m, 4H), 2.69 ppm (d, *J* = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 148.6, 147.7, 145.1, 129.5, 128.9, 128.2, 124.6, 123.8, 111.7, 111.2, 110.8, 60.1, 56.0, 55.9, 53.4, 40.7, 39.7, 37.0, 29.6 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 2964, 2846, 1632, 1595, 1458, 1329, 1254, 1106 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{21}H_{25}NO_6S$: 420.1475 $[M+H]^+$; found: 420.1479.

1,2,9,10-Tetramethoxy-6-(*m*-tolylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 c): White solid (90%); R_f (MeOH/CH_2Cl_2 5:95) = 0.60; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 3:97); mp: 207–209 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1H), 7.62–7.59 (m, 2H), 7.31–7.26 (m, 2H), 6.81 (s, 1H), 6.48 (s, 1H), 4.59–4.55 (m, 1H), 4.10 (d, *J* = 15.2 Hz, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 3.62 (s, 3H), 3.29 (t, *J* = 12.0 Hz, 1H), 3.13–3.09 (m, 1H), 3.03–2.96 (m, 1H), 2.46–2.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 148.5, 147.7, 144.9, 140.8, 139.5, 133.5, 129.6, 129.2, 128.1, 127.4, 127.4, 124.1, 123.9, 111.7, 111.3, 110.6, 60.1, 56.0, 55.9, 53.5, 41.2, 37.7, 29.8, 28.9, 21.5 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 2931, 2845, 1602, 1513, 1460, 1317, 1254, 1104 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{27}H_{29}NO_6S$: 496.1788 $[M+H]^+$; found: 496.1783.

1-(2-Ethoxy-1,9,10-trimethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]quinolin-6(5*H*)-yl)ethanone (27 d): White solid (77%); R_f (MeOH/CH_2Cl_2 5:95) = 0.65; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 2:98); mp: 219–221 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 8.18–8.15 (m, 1H), 6.77–6.76 (m, 1H), 6.64–6.61 (m, 1H), 5.08–4.93 (m, 1H), 4.12–4.08 (m, 2H), 4.00–3.97 (m, 1H), 3.93–3.90 (m, 6H), 3.67–3.66 (m, 3H), 3.33–2.61 (m, 5H), 2.21–2.17 (m, 3H), 1.51–1.47 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 169.2, 151.4, 148.3, 147.4, 145.2, 130.5, 129.9, 129.1, 128.0, 127.6, 125.8, 124.1, 111.7, 111.4, 64.2, 60.0, 56.0, 54.2, 50.7, 42.2, 36.6, 33.6, 30.8, 22.8, 15.1 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 2931, 1639, 1512, 1449, 1353, 1255, 1099 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{23}H_{27}NO_5$: 398.1962 $[M+H]^+$; found: 398.1967.

[2-Ethoxy-1,9,10-trimethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]quinolin-6(5*H*)-yl](phenyl)methanone (27 e): White solid (69%); R_f (MeOH/CH_2Cl_2 5:95) = 0.65; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 1:99); mp: 218–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1H), 7.43 (S, 5H), 6.79 (s, 1H), 6.62 (s, 1H), 4.13–4.07 (m, 3H), 3.91 (s, 6H), 3.69 (s, 3H),

3.27–3.21 (m, 3H), 2.89 (q, J=13.2 Hz„ 2H), 2.63–2.59 (m, 1H), 1.49 ppm (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.9, 151.5, 148.3, 147.5, 145.2, 136.9, 129.7, 129.3, 128.7, 128.0, 126.7, 125.4, 124.2, 111.8, 111.5, 111.3, 64.3, 60.0, 56.0, 55.9, 34.8, 29.8, 15.1 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=3292, 3053, 2921, 2852, 1713, 1604, 1428, 1151 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{28}H_{29}NO_5$: 460.2118 $[M+H]^+$; found: 460.2113.

2-Ethoxy-1,9,10-trimethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 f): White solid (91%); R_f ($MeOH/CH_2Cl_2$ 5:95)=0.60; purification by flash column chromatography (deactivated silica gel, $MeOH/CH_2Cl_2$ 2:98); mp: 241–242 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.14 (s, 1H), 6.78 (s, 1H), 6.62 (s, 1H), 4.49 (t, J=9.2 Hz, 1H), 4.12–4.07 (m, 2H), 3.92–3.90 (m, 6H), 3.67 (s, 3H), 3.30–3.23 (m, 1H), 2.99 (d, J=9.2 Hz, 2H), 2.89–2.87 (m, 3H), 2.67 (d, J=15.6 Hz, 1H), 1.50 ppm (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.8, 148.5, 147.7, 145.3, 129.4, 128.8, 128.2, 124.4, 123.9, 111.8, 111.7, 111.2, 64.3, 60.1, 56.1, 55.9, 53.4, 40.7, 39.7, 37.1, 29.6, 15.1 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=2929, 2851, 1631, 1514, 1419, 1355, 1256, 1102 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{22}H_{27}NO_6S$: 434.1632 $[M+H]^+$; found: 433.1638.

2-Ethoxy-1,9,10-trimethoxy-6-(*m*-tolylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 g): White solid (86%); R_f ($MeOH/CH_2Cl_2$ 5:95)=0.55; purification by flash column chromatography (deactivated silica gel, $MeOH/CH_2Cl_2$ 3:97); mp: 196–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.13 (s, 1H), 7.62–7.60 (m, 2H), 7.32–7.31 (m, 2H), 6.81 (s, 1H), 6.47 (s, 1H), 4.59–4.55 (m, 1H), 4.11–4.00 (m, 3H), 3.94 (s, 3H), 3.90 (s, 1H), 3.64 (s, 3H), 3.29 (t, J=11.6 Hz, 1H), 3.13–2.96 (m, 2H), 2.45–2.33 (m, 5H), 1.46 ppm (t, J=7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.6, 148.5, 147.6, 145.1, 140.8, 139.6, 133.5, 129.5, 129.3, 129.2, 128.1, 127.4, 124.5, 124.1, 124.0, 111.7, 111.5, 111.2, 64.2, 60.1, 56.1, 55.9. 53.5, 41.2, 37.7, 28.9, 21.5, 15.1 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=2927, 2849, 1735, 1632, 1515, 1467, 1336, 1252, 1099 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{28}H_{31}NO_6S$: 510.1945 $[M+H]^+$; found: 510.1949.

1-Ethoxy-2,9,10-trimethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 h): White solid (92%); R_f ($MeOH/CH_2Cl_2$ 5:95)=0.60; purification by flash column chromatography (deactivated silica gel, $MeOH/CH_2Cl_2$ 2:98); mp: 190–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.15 (s, 1H), 6.76 (s, 1H), 6.61 (s, 1H), 4.47–4.42 (m, 1H), 4.09–4.06 (m, 1H), 3.90–3.86 (m, 9H), 3.64–3.61 (m, 1H), 3.45–3.44 (m, 3H), 3.28–3.22 (m, 1H), 2.97–2.85 (m, 4H), 2.69–2.66 (m, 1H) 1.34–1.23 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.6, 148.4, 147.4, 144.1, 129.4, 128.7, 128.5, 124.6, 111.9, 111.1, 110.7, 68.7, 55.9, 55.9, 55.9, 53.4, 50.8, 40.7, 39.6, 37.1, 29.8, 15.9 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=2930, 2842, 1730, 1632, 1513, 1464, 1384, 1254, 1104 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{22}H_{27}NO_6S$: 434.1632 $[M+H]^+$; found: 433.1638.

1-Ethoxy-2,9,10-trimethoxy-6-(*m*-tolylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 i): White solid (88%); R_f ($MeOH/CH_2Cl_2$ 5:95)=0.65; purification by flash column chromatography (deactivated silica gel, $MeOH/CH_2Cl_2$ 2:98); mp: 230–231 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.15 (s, 1H), 7.62–7.59 (m, 2H), 7.31 (s, 2H), 6.81 (s, 1H), 6.47 (s, 1H), 4.55–4.52 (m, 1H), 4.10–4.07 (m, 1H), 3.94- 3.91(m, 10H), 3.64–3.60 (m, 1H), 3.32–2.95 (m, 3H), 2.46–2.36 (m, 5H), 1.31–1.27 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.4, 148.4, 147.4, 143.9, 140.8, 139.5, 133.5, 129.5, 129.2, 129.1, 128.5, 127.4, 124.7, 124.2, 124.1, 111.9, 111.2, 110.5, 68.7, 55.9, 55.9, 53.6, 41.2, 37.8, 28.9, 21.5, 15.9 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=2924, 2830, 1631, 1513, 1464, 1340, 1254, 1105 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{28}H_{31}NO_6S$: 510.1945 $[M+H]^+$; found: 510.1940.

2,9,10-Trimethoxy-6-(methylsulfonyl)-1-propoxy-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 j): White solid (83%); R_f ($MeOH/CH_2Cl_2$ 5:95)=0.60; purification by flash column chromatography (deactivated silica gel, $MeOH/CH_2Cl_2$ 2:98); mp: 185–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.14 (s, 1H), 6.78 (s, 1H), 6.62 (s, 1H), 4.45 (t, J=9.2 Hz, 1H), 4.12–4.08 (m, 1H), 3.92–3.88 (m, 9H), 3.78 (q, J=8.4 Hz, 1H), 3.55 (q, J=8.0 Hz, 1H), 3.26 (t, J=12.0 Hz, 1H), 2.99–2.97 (m, 2H), 2.89–2.87 (m, 4H), 2.71–2.67 (m, 1H), 1.77–1.68 (m, 2H), 0.92 ppm (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.5, 148.5, 147.5, 144.5, 129.4, 128.6, 128.5, 124.6, 124.1, 112.1, 111.1, 110.8, 74.9, 56.0, 55.9, 53.4, 40.7, 39.6, 37.2, 29.8, 29.8, 29.6, 23.8 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=2925, 2849, 1631, 1514, 1462, 1386, 1254, 1077 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{23}H_{29}NO_6S$: 448.1788 $[M+H]^+$; found: 448.1783.

2,9,10-Trimethoxy-1-propoxy-6-(*m*-tolylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 k): White solid (87%); R_f ($MeOH/CH_2Cl_2$ 5:95)=0.65; purification by flash column chromatography (deactivated silica gel, $MeOH/CH_2Cl_2$ 2.5:97.5); mp: 265–267 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.12 (s, 1H), 7.62–7.59 (m, 2H), 7.34–7.31 (m, 2H), 6.81 (s, 1H), 6.47 (s, 1H), 4.54 (dd, J=4.8,13.6 Hz 1H), 4.11–4.06 (m, 1H), 3.94–3.88 (m, 6H), 3.82 (s, 3H), 3.78–3.72 (m, 1H), 3.10 (dd, J=3.6, 14.0 1H), 2.99 (t, J=13.2 Hz, 1H), 2.36–2.34 (m, 5H), 1.77–1.65 (m, 2H), 0.90 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.3, 148.4, 147.4, 144.2, 140.8, 139.5, 133.5, 129.5, 129.2, 128.9, 128.4, 127.4, 124.8, 124.2, 124.1, 112.0, 111.1, 110.6, 75.0, 55.9, 55.9, 55.6, 41.2, 37.8, 29.8, 28.8, 23.7, 21.5, 10.5 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=2931, 1632, 1513, 1461, 1339, 1254, 1012 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{29}H_{33}NO_6S$: 524.2101 $[M+H]^+$; found: 524.2106.

1-[1-(Benzyloxy)-2,9,10-trimethoxy-6*a*,7-dihydro-4*H*-dibenzo-[*de*,*g*]quinolin-6(5*H*)-yl]ethanone (27 l): White solid (67%); R_f ($MeOH/CH_2Cl_2$ 5:95)=0.55; purification by flash column chromatography (deactivated silica gel, $MeOH/CH_2Cl_2$ 3:97); mp: 165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ=8.09–8.06 (m, 1H), 7.37–7.29 (m, 5H), 6.78–6.76 (m, 1H), 6.69–6.65 (m, 1H), 5.08–5.05 (m, 1H), 4.98–3.93 (m, 1H), 4.02–3.90 (m, 6H), 3.49 (s, 3H), 3.32 (t, J=12.4, 1H), 3.08–2.68 (m, 4H), 2.22–2.18 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ=169.2, 152.2, 148.2, 147.2, 143.8, 137.4, 130.7, 129.7, 129.4, 128.9, 128.7, 128.4, 128.2, 126.0, 124.9, 124.1, 112.1, 111.3, 110.6, 74.6, 56.1, 55.8, 55.5, 54.2, 50.8, 42.2, 36.2, 34.7, 33.6, 31.7, 30.9, 30.9, 30.0, 29.8, 26.9, 25.4, 22.8, 21.8, 20.8 ppm. FTIR (KBr): $\tilde{\nu}_{max}$=2929, 2840, 1737, 2852, 1621, 1510, 1432, 1392, 1221, 1027 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{28}H_{29}NO_5$: 460.2118 $[M+H]^+$; found: 460.2112.

[1-(Benzyloxy)-2,9,10-trimethoxy-6*a*,7-dihydro-4*H*-dibenzo[*de*,*g*]-quinolin-6(5*H*)-yl](phenyl)methanone (27 m): White solid (71%); R_f ($MeOH/CH_2Cl_2$ 5:95)=0.60; purification by flash column chromatography (deactivated silica gel, $MeOH/CH_2Cl_2$ 1.5:98.5); mp: 165–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.08 (s, 1H), 7.44–7.38 (m, 7H), 7.35–7.28 (m, 3H), 6.79(s, 1H), 6.66 (s, 1H), 4.92 (d, J=10.4 Hz, 1H), 4.55 (d, J=10.8 Hz, 1H), 4.12–4.02 (m, 1H), 3.92–3.91 (m, 6H), 3.50 (s, 3H), 3.25–3.12 (m, 2H), 2.97–2.80 (m, 3H), 2.67–2.60 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.9, 152.4, 148.3, 147.3, 143.8, 137.4, 136.9, 129.7, 129.7, 128.8, 128.7, 128.6, 128., 128.2, 126.8, 125.7, 124.1, 112.1, 112.2, 110.7, 74.6, 56.1, 55.7, 55.6, 51.4, 34.03, 43.5, 30.9, 29.8 ppm; FTIR (KBr): $\tilde{\nu}_{max}$=2926, 2856, 1738, 1625, 1508, 1421, 1217, 1024 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{33}H_{31}NO_5$: 522.2275 $[M+H]^+$; found: 522.2272.

1-(Benzyloxy)-2,9,10-trimethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 n): White solid (88%); R_f ($MeOH/CH_2Cl_2$ 5:95)=0.60; purification by flash column chroma-

tography (deactivated silica gel, MeOH/CH_2Cl_2 2:98); mp: 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1H), 7.37–7.28 (m, 5H), 6.78 (s, 1H), 6.66 (s, 1H), 4.91 (d, J = 10.0 Hz, 1H), 4.52–4.46 (m, 2H), 4.14–4.10 (m, 1H), 3.92 (s, 6H), 3.50 (s, 3H), 3.32–3.24 (m, 1H), 3.15–3.13 (m, 1H), 3.02–2.87 (m, 5H), 2.79–2.70 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.6, 148.4, 147.4, 143.9, 137.2, 129.3, 129.1, 128.8, 128.7, 128.4, 128.3, 124.6, 123.9, 112.1, 111.1, 110.9, 74.7, 56.1, 55.9, 55.6, 53.4, 46.1, 39.6, 37.1, 29.6 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 2932, 2838, 1738, 1581, 1510, 1448, 1383, 1011 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{27}H_{29}NO_6S$: 496.1788 $[M+H]^+$; found: 496.1782.

1-(Benzyloxy)-2,9,10-trimethoxy-6-(*m*-tolylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 o): White solid (90%); R_f (MeOH/CH_2Cl_2 5:95) = 0.65; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 1.5:98.5); mp: 119–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1H), 7.63–7.60 (m, 2H), 7.33–7.29 (m, 7H), 6.81 (s, 1H), 6.51 (s, 1H), 5.28 (s, 2H), 4.89 (t, J = 5.2 Hz, 1H), 4.58–4.45 (m, 2H), 4.10 (d, J = 14.0 Hz, 1H), 3.94–3.86 (m, 6H), 3.51 (s, 3H), 3.33–3.26 (m, 1H), 3.14–3.95 (m, 1H), 2.51–2.28 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 148.4, 147.4, 143.7, 140.7, 139.5, 137.2, 133.5, 129.4, 128.8, 128.4, 128.3, 127.3, 124.1, 112.0, 111.1, 110.7, 74.7, 55.9, 55.9, 55.6, 53.5, 41.2, 32.0, 28.8, 26.9, 14.2 ppm. FTIR (KBr): $\tilde{\nu}_{max}$ = 2929, 2856, 1737, 1591, 1449, 1339, 1249, 1001 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{33}H_{33}NO_6S$: 572.2101 $[M+H]^+$; found: 572.2106.

1-(Benzyloxy)-2,9,10-trimethoxy-6-methyl-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 p): Crude amine **26 c** (0.90 mmol, 1 equiv) and formaldehyde (30% aqueous solution, 1.84 mmol, 2 equiv) were dissolved in CH_2Cl_2 (15 mL), and the mixture was stirred at room temperature for 10 min. Sodium triacetoxyborohydride (4.61 mmol, 5.0 equiv) was added, and the mixture was stirred at room temperature overnight. The mixture was quenched with $NaHCO_3$ (5% aqueous solution, 10 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic phase was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (MeOH/CH_2Cl_2 1:99, *v/v*), which furnished **27 p** as a solid (67%): R_f (MeOH/CH_2Cl_2 5:95) = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1H), 7.33–7.23 (m, 5H), 6.75 (s, 1H), 6.59 (s, 1H), 4.88 (d, J = 14.4 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.54 (s, 3H), 3.20–2.97 (m, 4H), 2.70–2.65 (m, 1H), 2.60–2.48 ppm (m, 5H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2, 147.9, 147.3, 142.9, 137.3, 129.2, 129.1, 128.9, 128.3, 128.1, 127.7, 127.2, 124.6, 112.1, 110.7, 110.5, 74.9, 62.7, 55.9, 55.9, 55.7, 53.4, 44.1, 34.6, 29.3 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 2938, 2843, 1736, 1591, 1453, 1371, 1223, 1151 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{27}H_{29}NO_4$: 432.2169 $[M+H]^+$; found: 432.2163.

1-[2-(Benzyloxy)-1,9,10-trimethoxy-6*a*,7-dihydro-4*H*-dibenzo-[*de*,*g*]quinolin-6(5*H*)-yl]ethanone (27 q): White solid (70%); R_f (MeOH/CH_2Cl_2 5:95) = 0.60; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 2:98); mp: 165–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 8.19–8.16 (m, 1H), 7.49–7.32 (m, 5H), 6.78–6.67 (m, 2H), 5.17–4.93 (m, 3H), 3.99–3.9 (m, 7H), 3.71 (s, 3H), 3.32–2.65 (m, 5H), 2.21–2.18 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 169.3, 151.3, 148.4, 147.4, 145.5, 137.1, 129.9, 129.1, 128.7, 128.0, 127.4, 126.4, 125.3, 124.1, 112.3, 111.8, 111.4, 70.9, 60.2, 56.1, 50.8, 42.1, 31.7, 29.7, 22.8, 14.3 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 2927, 2852, 1737, 1636, 1509, 1422, 1249, 1025 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{28}H_{29}NO_5$: 460.2118 $[M+H]^+$; found: 460.2114.

2-(Benzyloxy)-1,9,10-trimethoxy-6-(methylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 r): White solid (91%); R_f (MeOH/CH_2Cl_2 5:95) = 0.65; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 2:98); mp: 175–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1H), 7.48–7.34 (m, 5H), 6.78 (s, 1H), 6.69 (s, 1H), 5.14(q, J = 12, 2H), 4.50 (t, J = 8.8, 1H), 4.12–4.07(m, 1H), 3.92–3.91(m, 6H), 3.71(s, 3H), 3.28–3.22 (m, 1H), 2.99 (d, J = 9.2, 2H), 2.90–2.83 (m, 4H), 2.67–2.63 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.7, 148.6, 147.7, 145.6, 136.9, 129.5, 128.9, 128.8, 128.4, 128.2, 127.4, 124.9, 123.9, 112.5, 111.7, 111.2, 70.9, 60.2, 56.1, 55.9, 53.3, 40.6, 39.7, 36.9, 29.6 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 2998, 2844, 1738, 1592, 1459, 1322, 1250, 1018 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{27}H_{29}NO_6S$: 496.1788 $[M+H]^+$; found: 496.1783.

2-(Benzyloxy)-1,9,10-trimethoxy-6-(*m*-tolylsulfonyl)-5,6,6*a*,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (27 s): White solid (88%); R_f (MeOH/CH_2Cl_2 5:95) = 0.60; purification by flash column chromatography (deactivated silica gel, MeOH/CH_2Cl_2 2:98); mp: 125–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1H), 7.62–7.60 (m, 2H), 7.45–7.31 (m, 7H), 6.81 (s 1H), 6.54 (s, 1H), 5.11–5.04 (m, 2H), 4.61–4.56 (m, 1H), 4.10–4.06 (m, 1H), 3.94–3.91 (m, 6H), 3.72–3.68 (m, 3H), 3.31–3.24 (m, 1H), 3.13–2.96 (m, 2H), 2.43–2.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.5, 148.5, 147.6, 145.4, 140.8, 139.5, 136.9, 133.5, 129.6, 129.2, 129.2, 128.7, 128.1, 127.4, 125.1, 124.1, 123.9, 112.2, 111.7, 111.2, 70.8, 60.2, 56.1, 55.9, 53.5, 41.1, 37.6, 28.8, 21.5 ppm; FTIR (KBr): $\tilde{\nu}_{max}$ = 2929, 2840, 1735, 1587, 1457, 1333, 1250, 1017 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{33}H_{33}NO_6S$: 572.2101 $[M+H]^+$; found: 572.2106.

Biological methods

Platelet aggregation inhibitory activity evaluation:[11a–c] Synthesized novel aporphine analogues **34 a–s** were dissolved in DMSO before testing. To eliminate the effects of the solvent on aggregation, the final concentration of DMSO was fixed at 0.5%. Arachidonic acid (AA), disodium ethylenediaminetetraacetate (Na_2EDTA), bovine serum albumin, and dimethyl sulfoxide (DMSO) were purchased from Sigma Chemical Co.

Platelet aggregation inhibitory bioassay: Blood was collected from the rabbit marginal ear vein (several studies established that rabbit platelets were surrogate to human platelets both in vitro and in vivo)[11d] and was mixed with Na_2EDTA to a final concentration of 6 mM. It was centrifuged for 10 min at 90 *g* at room temperature, and the supernatant was obtained as platelet-rich plasma. The latter was further centrifuged at 500 *g* for 10 min. The platelet pellets were washed with Tyrode's solution (Ca^{+2}-free) containing 2 mM Na_2EDTA (0.1 mg mL^{-1}) and bovine serum albumin (3.5 mg mL^{-1}) and was centrifuged at 500 *g* for 10 min. Then, the pellets were washed with Tyrode's solution without Na_2EDTA. After centrifugation under the same conditions, the platelet pellets were finally suspended in Tyrode's solution of the following composition: NaCl (136.8 mM), KCl (2.8 mM), $NaHCO_3$ (11.9 mM), $MgCl_2$ (2.1 mM), NaH_2PO_4 (0.33 mM), $CaCl_2$ (1.0 mM), and glucose (11.2 mM) containing bovine serum albumin (0.35%).

Aggregation was measured by a turbidimetric method by using a Lumi-aggregometer (Chrono-Log Corp., Havertown, PA, USA). All glassware was siliconized. Three minutes before the addition of the aggregation inducer, the platelet suspension was stirred at 1200 rpm. The percentage of aggregation was calculated as follows [Eq. (1)]:

$$\text{Aggregation}\,[\%] = \left(\frac{A_{\text{platelet suspension}} - A_{\text{final post-aggregation}}}{A_{\text{platelet suspension}} - A_{\text{Tyrode solution}}}\right) \times 100 \qquad (1)$$

Percent aggregation was expressed assuming the absorbance of platelet suspension ($A_{\text{platelet suspension}}$) as 0% aggregation and the absorbance of platelet-free Tyrode's solution ($A_{\text{Tyrode solution}}$) as 100% aggregation. For each compound, IC_{50} values were calculated by SigmaPlot.

In vitro antioxidant DPPH radical scavenging activity:[12a–e] In the DPPH radical-scavenging method, the sample at different concentrations ranging from 10 to 100 $\mu g\,mL^{-1}$ was mixed with a methanol solution of DPPH (20 $mg\,L^{-1}$, 1.5 mL). Pure methanol was taken as control and ascorbic acid (vitamin C) was used as a reference compound. The percent of DPPH decoloration of the sample was calculated according to Equation (2):

$$\text{Decoloration}\,[\%] = \left(1 - \frac{A_{\text{sample}}}{A_{\text{control}}}\right) \times 100 \qquad (2)$$

The decoloration was plotted against the sample concentration, and a logarithmic regression curve was established to calculate the IC_{50}. The results are expressed as antiradical efficiency (AE), which is 1000-fold inverse of the IC_{50} value [Eq. (3)]:

$$\text{AE} = \frac{1000}{IC_{50}} \qquad (3)$$

In silico molecular docking simulation studies

The molecular docking studies were performed by using SYBYL-X 2.1.1 software (Tripos International).[8a,13] The crystal structures of the antiplatelet target (PDB ID: 2OYE)[14] and antioxidant target (PDB ID: 3MNG)[15] co-crystallized with indomethacin (ligand ID: IM8) and dithiothreitol (ligand ID: DID), respectively, were used for the molecular docking studies. Prior to molecular docking, the protein structures were prepared by using a standard protocol for the structure preparation tool of the SYBYL-X suite that included addition of hydrogen atoms, assignment of charges (Amber7FF99:Protein/Gasteiger–Marsili:Ligand),[16] and side-chain optimization and minimization. The Surflex-Dock (SFCX) search algorithm2 was used to dock the co-crystallized ligand (ID: IM8, DID) and synthesized compounds. The ligands were prepared by the ligand preparation module of the SYBYL-X suite. To evaluate the molecular docking program parameters, each co-crystallized ligand was extracted from each crystal structure and redocked back into the active site of the proteins. During docking, the protein was kept rigid, whereas the ligand was treated as fully flexible. A protomol-based method[17] and empirically derived scoring function implemented in Surflex-Dock was used to calculate the interaction of the ligands and proteins. The scoring functions included hydrophobic, polar, repulsive, entropic, solvation, and crash terms. The Surflex-Dock scores are expressed in $-\log10\,(K_d)$ units to represent binding affinities.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · antioxidant activity · antiplatelet activity · radicals · structure–activity relationships

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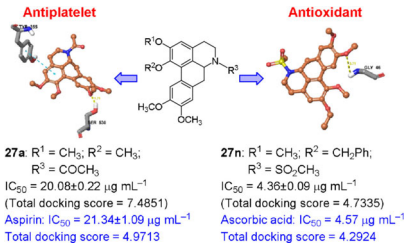
A familiar ring: Functionalized aporphine analogues with alkoxy functional groups at C1/C2 of ring A and an acyl or phenylsulfonyl functionality at the N6 position of ring B of the aporphine scaffold were synthesized and evaluated for their arachidonic acid induced antiplatelet aggregation inhibitory activity and free-radical-scavenging antioxidant activity. In silico molecular docking simulation studies of the active analogues were also performed.



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Discovery of Aporphine Analogues as Potential Antiplatelet and Antioxidant Agents: Design, Synthesis, Structure–Activity Relationships, Biological Evaluations, and in silico Molecular Docking Studies