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Design of novel nicotinic ligands through 3D database searching

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Abstract—A series of quinoline derivatives have been designed on the basis of results from a 3D search of the Cambridge Structural Database using the nicotinic pharmacophore as a query and further modified using molecular modeling. Some of the synthesized compounds show nanomolar affinity for the central nicotinic receptor on rat cerebral cortex.

1. Introduction

The nicotinic receptor is a subtype of cholinergic receptors belonging to the super family of Ligand Gated Ion Channels (LGIC),[1] made up of five subunits arranged to form a pore through which cations enter into cells.[2] With respect to the subunit composition, the best characterized types of nicotinic receptors are: (i) the $\alpha_2\beta\gamma\delta$ subtype, found at the neuromuscular junction; (ii) the $\alpha4\beta2$ subtype, the most abundant in the CNS of mammalians; (iii) the $\alpha3\beta4$ subtype, present at the ganglionic level and (iv) the $\alpha7$ subtype which, differently from the others, is homomeric.[3]

Nicotinic receptors are expressed in many tissues and play a role in several physiological functions. The therapeutic potential of nicotinic agonists is evidenced, not only by the variety of pharmacological effects elicited by nicotine and acetylcholine, but also by the various neuropsychiatric disorders in which nicotinic receptors appear to be involved.[4,5] The development of drugs acting through modulation of the nicotinic receptors is, however, hampered by the high number of receptor subtypes and, more importantly, by the lack of selective ligands.[6,7]

Many nicotinic agonists have been isolated by natural sources and have represented lead compounds for the design of new analogs. In recent years, it has been shown that 3D database searching is a valuable tool to discover novel lead compounds.[8] The input for the search engine is a query consisting in a set of distances among pharmacophoric features and other suitable 3D constraints. The query is typically built up from a pharmacophore model or, alternatively, from the structure of a highly active compound, which is rigid or whose bioactive conformation is known from X-ray or NMR experiments. The 3D search may end up with a number of hits, which are those structures within the database matching the query. If the number of hits is too high, the search can be repeated with a more selective query or the user can filter out less interesting structures by setting suitable cut off values of molecular weight, number of heteroatoms, calculated lipophilicity, number of rotatable bonds and other physico-chemical descriptors depending on the search engine and the database. Since hits may contain groups that hinder a correct interaction with the binding site, their structure is often simplified to get compounds with more chances of turning out active in the biological testing. In the literature there are several examples of the application of 3D searching approach.[9–11]

The nicotinic 'basic' pharmacophore consists of a cationic nitrogen (which can be a secondary or tertiary

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amine, or a quaternary ammonium group) and a hydrogen bond acceptor atom (typically a heteroaromatic ring nitrogen or a carbonyl oxygen). The spatial relationship between these two pharmacophoric elements is crucial for nicotinic activity.[12]

We have applied the 3D database searching approach to the design of new nicotinic ligands: the Cambridge Structural Database (CSD)[13] was scanned through a query consisting in a pharmacophore substructure with 3D constraints. Our working hypothesis was that pharmacophoric features of nicotinic agonists could be found in some of the structures deposited in the CSD, which have never been tested or even considered as nicotinic agonists.

A ligand de novo design approach to identify new nicotinic agonists has been reported by Sheridan and Venkataraghavan.[14] In the case study presented by these authors, a number of CSD structures were detected whose shapes fitted inside the union volume of overlapping nicotinic agonists (a volume somehow related the receptor binding cavity). The hits fulfilled only shape criteria and had to be subsequently converted, using interactive modeling techniques, into molecules satisfying pharmacophore requirements by mutating atom types (e.g., $CH_2 \rightarrow N–CH_3$, phenyl→pyridyl). In the quoted article, the designed structures were not synthesized and tested.

After the elucidation of the 3D structure of the Acetylcholine Binding Protein (AChBP)[15] and of some ligand–protein complexes[16] through X-ray crystallography,[17] preliminary models of the extracellular domain of the nicotinic receptor were proposed.[18–21] With respect to these models, it is worth pointing out that 3D database searching is a tool to design novel bioactive compounds and should not be regarded as a method to investigate the binding site at the molecular level. Consequently, the pharmacophoric features incorporated into the query may derive from any reasonable hypothesis and reflect, to different degrees, the actual nature of the binding site.

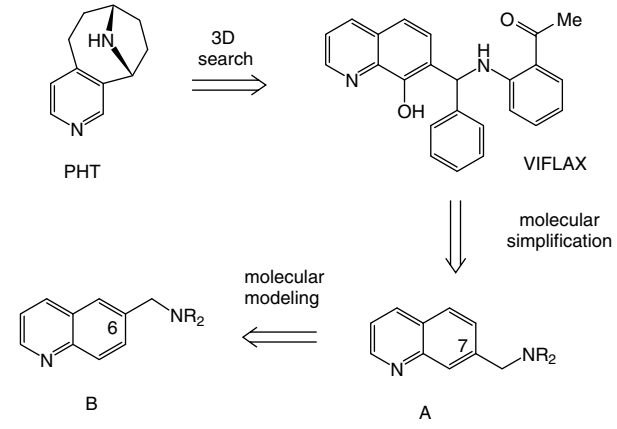


Chart 1.

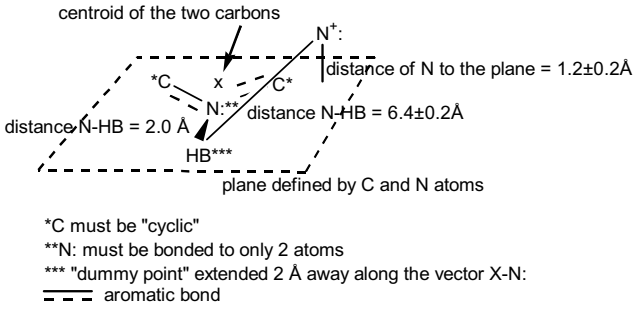


Figure 1. The query used to search the CSD.

2. Methodology

The CSD was scanned through the ConQuest search engine[22] using a query containing pharmacophoric features taken from the structure of pyrido[3,4-*b*]homotropane (PHT, Chart 1), a fully-rigid, high-affinity nicotinic agonist.[23] When tested as a racemic mixture, PHT exhibited an IC_{50} value of 5 nM (displacement of (−)-[^{3}H]-nicotine from rat brain homogenate).[23] A molecular model of PHT was built in the 1*R* configuration, according to Hacksell and Mellin,[24] and geometry optimized using the molecular mechanics cvff force-field implemented in the InsightII/Discover program.[25] The query (shown in Fig. 1) consisted of the following elements:

(i) a (potentially cationic) nitrogen (N^+);
(ii) a hydrogen bond acceptor nitrogen (N:) belonging to a heteroaromatic ring (the bonds in the C–N:–C substructure were defined 'aromatic');
(iii) a dummy point (HB) placed at 2.0 Å along the N: lone pair to simulate a hydrogen bond acceptor function within the binding site (the dummy point was defined as an extension of a vector pointing from the centroid of the two C atoms towards the N: atom);
(iv) a plane defined by the C–N:–C substructure.

In our geometry-optimized model of PHT, the distance between N^+ and HB was 6.4 Å and the height of N^+ from the heteroaromatic ring plane was 1.2 Å. Accordingly, the query was built up setting the above distances to the same values measured in the PHT model with a tolerance of ±0.2 Å. Additional constraints imposed on the search were: (i) N: had to be bonded only to the carbons of the substructure C–N:–C; (ii) the two C atoms had to be part of cyclic systems. Finally, the search was performed by discarding all the organometallic structures.

Chart 1 illustrates the steps of lead design. The result of the search were 125 hits, among which also nicotine was found (refcode DOXSIS). Among the output structures, the quinoline derivative VIFLAX[26] (Chart 1) attracted our interest because in this molecule the nicotinic phar-

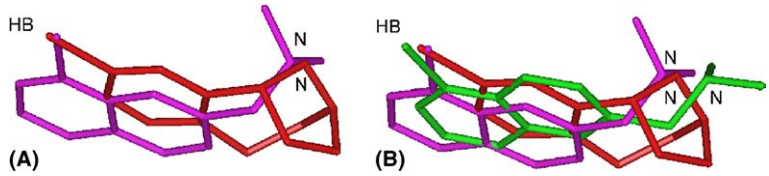


Figure 2. (A) Overlap of PHT and compound **1**. (B) Overlap of PHT, **1** and **2**. Hydrogen atoms are omitted. PHT: red, **1**: magenta, **2:** green. Molecular models were aligned as described in the Molecular Modelling part of Section 6.

macophore is arranged into a simple scaffold. VIFLAX structure was further simplified to the quinoline derivatives with general formula **A**, thought to be a more suitable lead compound in terms of synthetic accessibility, chemical stability, molecular weight and overall lipophilicity. Moreover, molecular modeling studies indicated that shifting the aminomethyl side chain of **A** from position 7 to position 6 of the quinoline ring would give compounds of general formula **B**, which could superimpose well on the template molecule PHT (Fig. 2, exemplified for R = Me).

During this research, however, we found that only 6-quinoline derivatives **B** (such as compound **2**) showed some affinity for the nicotinic receptor while derivative **A** (i.e., compounds **1**) turned out to be inactive. Therefore, further modifications were carried out only on 6-aminomethylquinolines **B**, such as demethylation, to give **3**, homologation, to give **4**, or cyclization, to give **5**. The amine **6** was tested since it was obtained in the synthesis of **1**. In addition, we also thought it was worth testing the methiodide of all compounds.

3. Chemistry

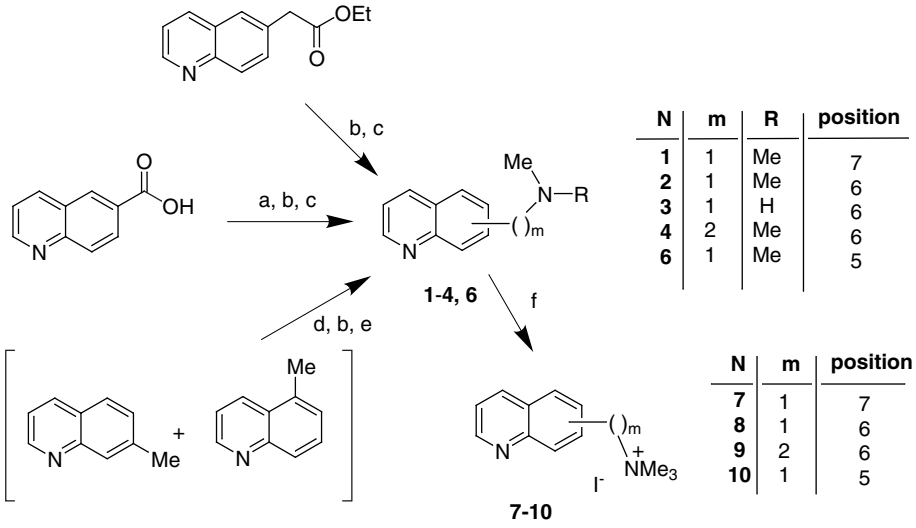
The synthetic pathways to obtain the aminoalkylquinoline derivatives are reported in Scheme 1. Amines **2**,[27] **3** and **4** were synthesized by $LiAlH_4$ reduction of the corresponding amides, prepared through standard methods from quinoline-6-carboxylic acid[28] and from ethyl 6-quinolinylacetate.[29] For the synthesis of **1** and **6** a mixture of 5- and 7-methylquinoline[30] was treated with N-bromosuccinimide and then with dimethylamine; after chromatographic separation, the two isomeric amines were obtained in good yields. Methiodides **7**–**10** were obtained by treatment of the tertiary amines with MeI.

The synthesis of the pyrrolidinyl derivatives **5**, **16** and **17** is reported in Scheme 2. The alcohol **11**, prepared through the Sonogashira reaction between 6-bromoquinoline[31] and 3-butyn-1-ol, was transformed into the mesilate **12** and reacted with ammonia, obtaining the amine **13**, together with the product of elimination **14**; cyclization with $PdCl_2$[32] afforded the immine **15**, which was reduced with $NaBH_4$ to **16**. The N-methyl derivative **5** was obtained by reaction with benzyl chloroformate and subsequent reduction with $LiAlH_4$; the methiodide **17** was prepared by reaction of **5** with methyl iodide.

4. Results

The synthesized compounds were tested in vitro on rat brain homogenates to evaluate their affinity for the central nicotinic receptors;[33] [^{3}H]-cytisine, believed to label $\alpha_4\beta_2$, which represents up to 90% of the high affinity agonist binding sites in rat brain,[34] was used as the radioligand.

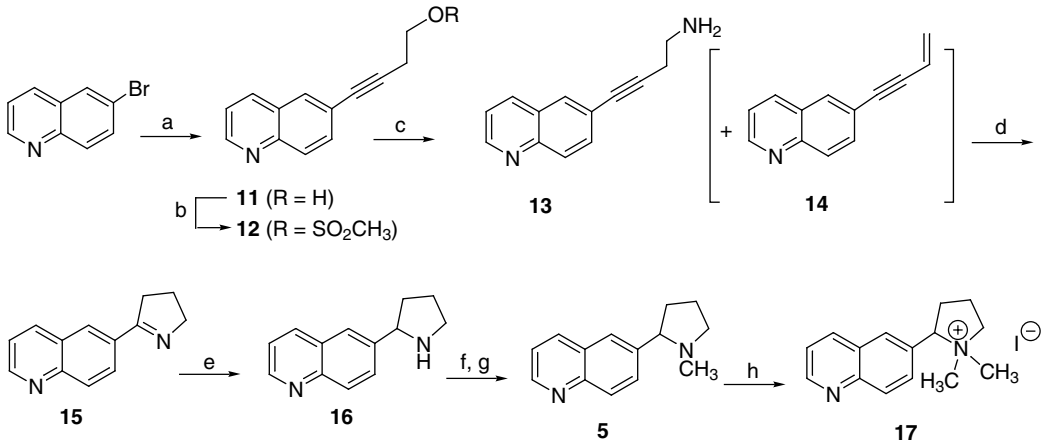
The affinity of the synthesized compounds for the central nicotinic receptor is reported in Table 1. Among the aminoalkylquinolines, only the 6-dimethylaminomethylquinoline **2** shows some affinity for the central nicotinic receptor, while the 5- or 7-substituted isomers



N	m	R	position
1	1	Me	7
2	1	Me	6
3	1	H	6
4	2	Me	6
6	1	Me	5

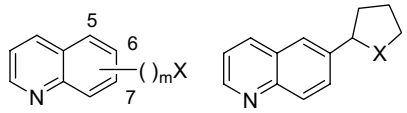
N	m	position
7	1	7
8	1	6
9	2	6
10	1	5

Scheme 1. Reagents and conditions: (a) $SOCl_2$; (b) $MeNH_2$ or Me_2NH; (c) $LiAlH_4$; (d) NBS, AIBN; (e) chromatographic separation; (f) MeI.



Scheme 2. Reagents and conditions: (a) 3-butyn-1-ol, $(PPh_3)_4Pd(0)$, CuBr; (b) MsCl, Py; (c) NH_3, MeOH; (d) $PdCl_2$, CH_3CN, H_2O; (e) $NaBH_4$; (f) ClCOOBz, NaOH, Na_2CO_3; (g) $LiAlH_4$; (h) CH_3I.

Table 1. Binding affinity[a] of compounds **1**–**9**, **16**, **17**



I II

N	Structure	X	m	Position	K_i (nM)
1	I	NMe_2	1	7	>10.000
2	I	NMe_2	1	6	6000 ± 497
3	I	NHMe	1	6	>10.000
4	I	NMe_2	2	6	>10.000
6	I	NMe_2	1	5	>10.000
7	I	NMe_3I	1	7	>10.000
8	I	NMe_3I	1	6	150 ± 6
9	I	NMe_3I	2	6	>10.000
10	I	NMe_3I	1	5	>10.000
5	II	NMe	—	6	132 ± 8
16	II	NH	—	6	7433 ± 510
17	II	NMe_2I	—	6	45 ± 2
Nicotine					8.2 ± 0.5[b]

[a] On rat cortical membranes. The nicotinic receptors were labelled by [^{3}H]-cytisine; see Ref. 42.
[b] From Ref. 33.

(compounds **6** and **1**, respectively) do not displace [^{3}H]-cytisine from its binding site. The lack of affinity of these compounds probably depends on ligand/receptor steric conflicts. This result is not surprising since the 3D query used to search the CSD database did not include shape-related factors. The reduction of the steric hindrance on the nitrogen, that is, removal of one methyl group to give **3**, or homologation to the dimethylaminoethyl analogue **4** resulted in a complete loss of affinity. The cyclization of the alkylamino group into a pyrrolidine ring (compound **5**) resulted in a 45-fold increase in affinity, and also the secondary base **16** shows affinity for the central nicotinic receptor, although with micromolar affinity.

The introduction of a permanent positive charge on active tertiary bases **2** and **5** resulted in a 40-fold and 3-fold increase of affinity (compounds **8** and **17**, respectively). The same modification on amines **1**, **3** and **6** was, however, ineffective.

5. Discussion

The 3D database search is a valuable tool to discover new leads. Recent applications of this approach have allowed the identification of new molecules interacting with receptors,[35] neurotransmitter's transporters,[11] or enzymes.[36] As briefly summarized in the Introduction, Sheridan and Venkataraghavan applied a shape-based 3D database searching algorithm to design new nicotinic agonists.[14] In their de novo design method, each hit represents a 'candidate' whose backbone must be chemically modified through a sort of atom type mutation to yield a

potentially active ligand. Differently from the de novo design methods, typical 3D database searching approaches identify hits, which are 'real' compounds (filed in the database as experimental or calculated structures), which can be synthesized according to published recipes or even directly tested if there are available samples. Although hits can be modified (as we actually did in the present work), users generally limit their intervention to molecular simplification consisting in removing bulky side chains while leaving unchanged the basic scaffold.

Our query for the 3D database scan of the CSD (Fig. 1) was based on the essential features of the nicotinic pharmacophore, extracted from the fully-rigid, high-affinity ligand PHT: the cationic nitrogen and the hydrogen bond acceptor nitrogen of the heteroaromatic ring. Differently from the Sheridan approach, the search was carried out applying 3D constraints so as to yield molecules having the pharmacophoric moieties in a specific spatial disposition.

The results of our 3D search suggested, among other structures, the 7-aminomethylquinoline moiety of A (Chart 1) as a simple scaffold to design new compounds endowed with affinity at the nicotinic receptor. Other nicotinic ligands containing the quinoline ring have already been reported in the literature: Glennon and coworkers showed that 5-dimethylaminoquinoline was able to displace [^{3}H]-nicotine from the nicotinic receptor in rat brain homogenate (K_i 450 nM),[37] while 5-ethylamino-5,6,7,8-tetrahydroquinoline and its N-methyl derivative are devoid of affinity.[38]

Preliminary optimization of **A** led to the 6-(dimethylaminomethyl)quinoline **2** (structure B), which was in turn further modified. It is known that the introduction of conformational constraints into the basic part of the molecule could improve potency, as demonstrated by the increase in affinity when going from 3-(dimethylamino)methylpyridine to nicotine;[39] also for the quinoline derivative **2**, this modification led to **5** with a substantial (45-fold) increase of affinity.

Quaternarization of the basic nitrogen of nicotinic ligands has different effect on affinity, producing in some cases an increase and in others a decrease of affinity.[40] For instance, on bulky ligands such as anatoxin-a[41] this modification greatly reduces affinity, while on other compounds, such as DMPP analogs, affinity is largely increased.[42] For the compounds synthesized in this work the increase is different if we consider cyclic or linear derivatives. In fact, methylation of the pyrrolidine derivative **5** gave only a 3-fold increase in affinity; the same modification on nicotine also led to a small (2-fold) increase.[37] Quaternarization of **2** gave a 40-fold increase of affinity: a similar large shift has also been found for some 3-(aminoethoxy)pyridines,[43] but not for 3-(dimethylamino)methylpyridine, where this modification led to only a 5-fold increase.[37] These differences may reflect a different mode of binding of the quaternary ammonium ligands to the nicotinic receptor with respect to their amino derivatives and/or different steric effects within the binding site.[42,44]

In conclusion, through 3D database searching ad molecular modeling we have designed a new series of nicotinic ligands, among which 6-(1-methylpyrrolidin-2-yl)quinoline (**5**) shows good affinity for the central nicotinic receptor and may represent a new lead for drug optimization. Compound **5** possesses a stereogenic center; although it would be interesting to also test its enantiomers, as pyrrolidine derivatives show enantioselectivity in the interaction with the nicotinic receptor, we thought it wise to study the enantioselectivity only after further improvement of affinity. Work is in progress in this direction and also to test the selectivity of the most interesting quinoline derivatives for nicotinic receptor subtypes.

6. Experimental

6.1. Chemistry

6.1.1. General considerations. All melting points were taken on a Büchi apparatus and are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 681 spectrophotometer in Nujol mull for solids and neat for liquids. NMR spectra were recorded on a Gemini 200 spectrometer (200 MHz for ^{1}H NMR, 50 MHz for ^{13}C) and on a Brucker Avance 400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C); chromatographic separations were performed on a silica gel column by gravity chromatography (Kieselgel 40, 0.063–0.200 mm; Merck) or flash chromatography (Kieselgel 40, 0.040–0.063 mm; Merck). Yields are given after purification, unless otherwise stated. Where analyses are indicated by symbols, the analytical results are within ±0.4% of the theoretical values.

6.1.2. 6-(Methylamino)methylquinoline (3). Quinoline-6-carboxylic acid[28] (0.3 g, 1.7 mmol) was heated with $SOCl_2$ (3 mL) at 60 °C for 9 h. After removal of the excess thionyl chloride under vacuum, the residue was treated, at 0 °C, with an excess (4 mL) of a 35% aqueous solution of $MeNH_2$. The solution was allowed to warm to room temperature, then it was extracted with CH_2Cl_2; drying (Na_2SO_4) and removal of the solvent gave N-methyl-quinoline-6-carboxyamide as an oil (79% yield). [^{1}H] NMR (200 MHz, $CDCl_3$, δ): 3.01 (s, 3H) (NCH_3); 4.79 (s, 1H, NH); 7.35 (dd, J = 8.4 Hz, 4.2 Hz, 1H, H-3); 7.99–8.12 (m, 3H, H-4 + H-7 + H-8); 8.24 (s, 1H, H-5); 8.93 (d, J = 4.2 Hz, 1H, H-2) ppm. To a solution of N-methyl-quinoline-6-carboxyamide (0.25 g, 1.34 mmol) in anhydrous THF, kept at 0 °C, $LiAlH_4$ (0.05 g, 1.34 mmol) was added. After stirring at room temperature for 7 h, the excess hydride was destroyed with ice and the solvent was evaporated under vacuum. The residue was treated with H_2O and extracted with $CHCl_3$. Drying (Na_2SO_4) and removal of the solvent gave a residue, which was purified by column chromatography ($CHCl_3$/CH_3OH 85:15 as eluent), obtaining the title compound in 38% yield. [^{1}H] NMR (200 MHz, $CDCl_3$, δ): 2.39 (s, 3H, NCH_3); 3.79 (s, 2H, CH_2N); 4.82 (s, 1H, NH); 7.07 (dd, J = 8.4 Hz, 4.0 Hz, 1H, H-3); 7.52–7.67 (m, 2H, H-5 + H-7); 7.93–8.06 (m, 2H, H-4 + H-8); 8.75–8.80 (d, J = 4.0 Hz, 1H, H-2) ppm.

[^{13}C] NMR (50 MHz, $CDCl_3$, δ): 36.28 (q); 55.93 (t); 121.45 (d); 126.46 (d); 128.42 (s); 129.61 (d); 130.45 (d); 136.14 (d); 138.75 (s); 147.84 (s); 150.22 (d) ppm. Anal. ($C_{11}H_{12}N_2$) C, H, N.

6.1.3. 6-(Dimethylamino)methylquinoline (2).[27] Following the same procedure described for N-methyl-quinoline-6-carboxyamide, using a 40% aqueous solution of Me_2NH, *N*,*N*-dimethyl-quinoline-6-carboxyamide was obtained as an oil (78% yield). [^{1}H] NMR (200 MHz, $CDCl_3$, δ): 2.92 (s, 3H, NCH_3); 3.16 (s, 3H, NCH_3); 7.39 (dd, J = 8.4 Hz, 4.2 Hz, 1H, H-3); 7.71 (d, J = 8.4 Hz, 1H, H-7); 7.87 (s, 1H, H-5); 8.03–8.20 (m, 2H, H-4 + H-8); 8.91 (d, J = 4.2 Hz, 1H, H-2) ppm.

Following the same procedure described for 6-(methylamino)methylquinoline, starting from *N*,*N*-dimethyl-quinoline-6-carboxyamide, the title compound was obtained in 54% yield. [^{1}H] NMR (400 MHz, $CDCl_3$, δ): 2.30 (s, 6H, $N(CH_3)_2$); 3.62 (s, 2H, CH_2N); 7.39 (dd, J = 8.0 Hz, 4.4 Hz, 1H, H-3); 7.70–7.74 (m, 2H, H-5 + H-7); 8.07 (d, J = 8.4 Hz, 1H, H-8); 8.13 (d, J = 8.0 Hz, 1H, H-4); 8.89 (dd, J = 4.4 Hz, 1.6 Hz, 1H, H-2) ppm. [^{13}C] NMR (50 MHz, $CDCl_3$, δ): 45.75 (q); 64.34 (t); 121.45 (d); 127.61 (d); 128.39 (s); 129.61 (d); 131.21 (d); 136.18 (d); 137.47 (s); 148.00 (s); 150.35 (d).

This compound was transformed into the oxalate salt by treatment with 1 equiv oxalic acid in ethyl acetate: mp 110 °C.

6.1.4. 7-(Dimethylamino)methylquinoline (1) and 5-(dimethylamino)methylquinoline (6). A mixture of 5- and 7-methylquinoline, (0.5 g, 3.5 mmol) (prepared as described by Palmer),[30] N-bromosuccinimide (0.62 g, 1 equiv) and α,α'-azoisobutyronitrile (AIBN, 0.02 g) in CCl_4 (30 mL) were kept under reflux for 6 h. The solvent was then removed under vacuum, the residue was treated with Me_2NH (6 mL of a 33% solution in EtOH) and the mixture was kept at room temperature for one night. After removal of the solvent, the residue was purified by column chromatography ($CHCl_3$/CH_3OH 9:1 as eluent) obtaining the two isomeric amines.

Compound **1**: oil, 28% yield. [^{1}H] NMR (200 MHz, $CDCl_3$, δ): 2.30 (s, 6H, $N(CH_3)_2$); 3.64 (s, 2H, CH_2N); 7.38 (dd, 1H, J = 8.2 Hz, 4.0 Hz, H-3); 7.60 (d, 1H, J = 8.4 Hz) and 7.79 (d, 1H, J = 8.4 Hz) (H-5 and H-6); 7.96 (s, 1H, H-8); 8.14 (d, 1H, J = 8.2 Hz, H-4); 8.90 (d, 1H, J = 4.0 Hz, H-2) ppm. [^{13}C] NMR (50 MHz, $CDCl_3$, δ): 45.81 (q); 64.69 (t); 121.21 (d); 127.84 (s); 128.15 (d); 128.28 (d); 129.43 (d); 136.13 (d); 140.82 (s); 148.55 (s); 150.77 (d) ppm. Anal. ($C_{12}H_{14}N_2$) C, H, N. This compound was transformed into the oxalate salt by treatment with 1 equiv oxalic acid in ethyl acetate: mp 140 °C.

Compound **6**: oil, 32% yield. [^{1}H] NMR (200 MHz, $CDCl_3$, δ): 2.31 (s, 6H, $N(CH_3)_2$); 3.87 (s, 2H, CH_2N); 7.41–7.49 (m, 2H, H-3 + H-6), 7.65 (dd, 1H, J = 8.4 Hz, H-7), 8.07 (d, 1H, J = 8.4 Hz, H-4), 8.66 (d, 1H, J = 8.4 Hz, H-8), 8.93 (d, 1H, J = 4.4 Hz, H-2). [^{13}C] NMR (50 MHz, $CDCl_3$, δ): 45.92 (q), 62.53 (t), 121.20 (d), 128.02 (s), 128.13 (d), 128.97 (d), 129.70 (d), 133.63 (d), 135.69 (s), 149.00 (s), 150.40 (d) ppm. Anal. ($C_{12}H_{14}N_2$) C, H, N. This compound was transformed into the oxalate salt by treatment with 1 equiv oxalic acid in ethyl acetate: mp 130 °C.

6.1.5. 6-[2-(Dimethylamino)ethyl]quinoline (4). Ethyl 6-quinolineacetate (0.6 g, prepared as described by Jones)[29] and a 50% toluene solution of Me_2NH (10 mL) were kept at 70 °C in a stainless steel vessel for 24 h. After removal of the solvent, the residue was purified by column chromatography ($CHCl_3$/MeOH 97:3 as eluent) obtaining *N*,*N*-dimethyl-quinoline-6-acetamide as an oil in 23% yield. [^{1}H] NMR (200 MHz, $CDCl_3$, δ): 2.97 (s, 3H, NCH_3); 3.02 (s, 3H, NCH_3); 3.87 (s, 2H, $COCH_2$); 7.35 (dd, J = 6.3 Hz, 4.4 Hz, 1H, H-3); 7.58–7.65 (m, 2H, H-5 + H-6); 8.02–8.10 (m, 2H, H-4 + H-8); 8.85 (d, J = 4.4 Hz, 1H, H-2) ppm.

This compound was reduced with $LiAlH_4$ as described for **3**, obtaining the title compound in 40% yield. [^{1}H] NMR (200 MHz, $CDCl_3$, δ): 2.34 (s, 6H, $N(CH_3)_2$); 2.59–2.70 (m, 2H); 2.94–3.01 (m, 2H); 7.38 (dd, J = 6.3 Hz, 4.0 Hz, 1H, H-3); 7.54–7.64 (m, 2H, H-5 + H-6); 8.00–8.12 (m, 2H, H-8 + H-4); 8.86 (d, 1H, J = 4.0 Hz, H-2) ppm. [^{13}C] NMR (50 MHz, $CDCl_3$, δ): 34.63 (t); 45.86 (q); 61.54 (t); 121.45 (d); 126.88 (d); 128.64 (s); 129.72 (d); 131.32 (d); 135.91 (d); 139.10 (s); 147.47 (s); 150.08 (d) ppm. Anal. ($C_{13}H_{16}N_2$) C, H, N.

This compound was transformed into the oxalate salt by treatment with 1 equiv oxalic acid in ethyl acetate: mp 190 °C.

6.1.6. General procedure for the synthesis of methiodides. To a solution of the suitable amine (0.05–0.1 g) in anhydrous diethyl ether (10–30 mL) CH_3I (1–2 mL) was added and the mixture was kept under stirring at room temperature for 12 h in the dark. The precipitate was then collected by filtration. In this way the following compounds were prepared.

6.1.6.1. *N*,*N*,*N*-Trimethyl(quinolin-7-yl)methanaminium iodide (7). 54% yield. Mp 205 °C. [^{1}H] NMR (200 MHz, D_2O, δ): 2.96 (s, 9H, $^+N(CH_3)_3$); 4.49 (m, 2H, CH_2N); 7.38–7.49 (m, H-3 + H-4); 7.82 (d, 1H, J = 8.4 Hz, H-5); 7.88 (s, 1H, H-8); 8.19 (d, 1H, J = 8.4 Hz, H-6), 8.66 (dd, 1H, J = 4.4 Hz, 1.8 Hz, H-2) ppm. Anal. ($C_{13}H_{17}IN_2$) C, H, N.

6.1.6.2. *N*,*N*,*N*-Trimethyl(quinolin-6-yl)methanaminium iodide (8). 29% yield. Mp 180 °C. [^{1}H] NMR (400 MHz, $CDCl_3$, δ): 3.47 (s, 9H, $^+N(CH_3)_3$); 5.33 (s, 2H, CH_2N); 7.50 (dd, J = 8.4 Hz, 4.0 Hz, 1H, H-3); 7.90 (dd, J = 8.8 Hz, 1.8 Hz, 1H, H-7); 8.19 (d, J = 8.8 Hz, 1H, H-8); 8.31 (d, J = 8.8 Hz, 1H, H-4); 8.34 (d, J = 1.8 Hz, 1H, H-5); 9.01 (dd, J = 4.0 Hz, 1.6 Hz, 1H, H-2) ppm. Anal. ($C_{13}H_{17}IN_2$) C, H, N.

6.1.6.3. *N*,*N*,*N*-Trimethyl-2-(quinolin-7-yl)ethanaminium iodide (9). 58% yield. Mp 170 °C. [^{1}H] NMR (200 MHz, D_2O, δ): 3.06 (s, 9H, $^+N(CH_3)_3$); 3.15–3.24

(m, 2H); 3.48–3.57 (m, 2H); 7.37–7.42 (m, 1H); 7.56 (d, 1H, $J = 8.4$ Hz); 7.71 (s, 1H, H-8); 7.84 (d, 1H, $J = 8.4$ Hz); 8.18 (d, 1H, $J = 8.8$ Hz); 8.64 (m, 1H, H-2) ppm. Anal. ($C_{14}H_{19}IN_2$) C, H, N.

6.1.6.4. *N,N,N*-Trimethyl(quinolin-5-yl)methanaminium iodide (10). 50% yield. Mp 200 °C. [^{1}H] NMR (200 MHz, D_2O, δ): 2.94 (s, 9H, $^+N(CH_3)_3$); 4.82 (m, 2H, CH_2N); 7.49 (dd, $J = 6.6$ Hz, 4.4 Hz, 1H, H-3); 7.62–7.71 (m, 2H), 7.98 (dd, 1H, $J = 6.0$ Hz, 4.0 Hz), 8.50 (d, 1H, $J = 8.1$ Hz, H-8), 8.69 (d, 1H, $J = 4.4$ Hz, H-2). Anal. ($C_{13}H_{17}IN_2$) C, H, N.

6.1.7. 4-(Quinolin-6-yl)-3-butyn-1-ol (11). To a solution of 6-bromoquinoline (1.73 g, 8.32 mmol) and 3-butyn-1-ol (1.16 g, 16.6 mmol) in anhydrous Et_3N (20 mL), palladium-tetrakis(triphenylphosphine) (0.38 g) and CuBr (0.14 g) were added and the mixture heated at 90 °C for 70 min. After cooling, the mixture was partitioned between a saturated solution of NH_4Cl and Et_2O; the aqueous layer was made alkaline and extracted with Et_2O. After drying (Na_2SO_4) and removal of the solvent under vacuum, the title compound was obtained in 82% yield as a white solid. Mp 70–71 °C. [^{1}H] NMR (400 MHz, $CDCl_3$, δ) 2.53 (br s, 1H, OH), 2.76 (t, 2H, $J = 6.3$ Hz, $CH_2C{\equiv}C$), 3.88 (br s, 2H, CH_2O), 7.39 (dd, 1H, $J = 8.3$ Hz, 4.2, H-3), 7.66 (d, 1H, $J = 8.7$ Hz, H-7), 7.86 (s, 1H, H-5), 8.01 (d, 1H, $J = 8.7$ Hz, H-8), 8.07 (d, 1H, $J = 8.2$ Hz, H-4), 8.88 (d, 1H, $J = 4.2$ Hz, H-2) ppm. [^{13}C] NMR (50 MHz, $CDCl_3$, δ) 23.88 (t), 60.78 (t), 81.42 (s), 88.23 (s), 121.55 (d), 121.99 (s), 127.87 (s), 128.84 (d), 130.86 (d), 132.52 (d), 135.91 (d), 146.89 (s), 15.033 (d) ppm. GC-MS (EI) M (%): 197 (47), 167 (47), 166 (100), 140 (24), 139 (30), 63 (22). Anal. ($C_{13}H_{11}NO$) C, H, N.

6.1.8. 4-(Quinolin-6-yl)-3-butynyl methanesulfonate (12). To a solution of **11** (0.2 g, 1.05 mmol) and pyridine (0.7 mL) in amylene-stabilized $CHCl_3$ (3 mL), cooled at 0 °C, methanesulfonyl chloride (1.14 g, 1.2 equiv) was added dropwise and the mixture was allowed to warm to room temperature. After 2 h stirring at this T, the mixture was treated with water and extracted in $CHCl_3$. The organic solvent was evaporated, the residue was treated with 0.1 M HCl and extracted with Et_2O; the aqueous layer was alkalinized with NaOH 10% and extracted again with $CHCl_3$. Drying (Na_2SO_4) and removal of the solvent gave the title compound as an oil in 96% yield. [^{1}H] NMR (400 MHz, $CDCl_3$, δ) 2.95 (t, 2H, $J = 6.7$ Hz, $CH_2C{\equiv}C$), 3.10 (s, 3H, CH_3SO_3), 4.44 (t, 2H, $J = 6.7$ Hz, CH_2O), 7.41 (dd, 1H, $J = 8.3$ Hz, 4.2 Hz, H-3), 7.68 (dd, 1H, $J = 8.6$ Hz, 1.7 Hz, H-7), 7.90 (d, 1H, $J = 1.4$ Hz, H-5), 8.03 (d, 1H, $J = 8.7$ Hz, H-8), 8.10 (d, 1H, $J = 8.3$ Hz, H-4), 8.91 (dd, 1H, $J = 4.4$ Hz, 1.6 Hz, H-2) ppm. Anal. ($C_{14}H_{13}NO_3S$) C, H, N.

6.1.9. 4-(Quinolin-6-yl)-3-butyn-1-amine (13). A mixture of **12** (7.12 g, 0.026 mol) and NH_3 (130 mL, 33% in water) in isopropanol (100 mL) was heated at 60 °C for 18 h. The solvent was removed under vacuum and the residue partitioned between H_2O and CH_2Cl_2; the organic layer was collected and dried (Na_2SO_4), then the solvent was evaporated, obtaining a mixture of the title compound and 6-(but-3-en-1-ynyl)quinoline **14**, which was separated by flash chromatography (using abs. EtOH/CH_2Cl_2/Et_2O/Pet. ether/NH_4OH 180:360:360:900:9.9 as eluent). The aqueous layer was alkalinized and extracted again with CH_2Cl_2; after drying (Na_2SO_4) and removal of the solvent, the title compound (2.98 g) was obtained as a yellowish oil.

Compound **13** (total yield 73%) [^{1}H] NMR (400 MHz, $CDCl_3$, δ) 2.62 (t, 2H, $J = 6.4$ Hz, $CH_2C{\equiv}C$), 2.98 (t, 2H, $J = 6.4$ Hz, CH_2N), 7.40 (dd, 1H, $J = 8.3$ Hz, 4.2 Hz, H-3), 7.69 (dd, 1H, $J = 8.7$ Hz, 1.8 Hz, H-7), 7.89 (d, 1H, $J = 1.4$ Hz, H-5), 8.02 (d, 1H, $J = 8.7$ Hz, H-8), 8.10 (d, 1H, $J = 7.9$ Hz, H-4), 8.89 (dd, 1H, $J = 4.0$ Hz, 1.6 Hz, H-2) ppm. [^{13}C] NMR (50 MHz, $CDCl_3$, δ) 24.68 (t), 42.64 (t), 81.71 (s), 89.50 (s), 121.70 (d), 122.05 (s), 128.05 (s), 129.52 (d), 130.98 (d), 132.48 (d), 135.68 (d) 147.53 (s), 150.78 (d) ppm. Anal ($C_{13}H_{12}N_2$) C, H, N.

Compound **14** (19% yield) [^{1}H] NMR (200 MHz, $CDCl_3$, δ) 5.56 (dd, 1H, $J = 2.2$, 11.0 Hz, ═C*H*H), 5.76 (dd, 1H, $J = 17.4$ Hz, 2.2 Hz, ═CH*H*), 6.03 (dd, 1H, $J = 17.4$ Hz, 10.6 Hz, CH═), 7.33 (dd, 1H, $J = 8.4$ Hz, 4.4 Hz, H-3), 7.68 (dd, 1H, $J = 8.8$ Hz, 1.8 Hz, H-7), 7.86 (d, 1H, $J = 1.5$ Hz, H-5), 8.00 (d, 1H, $J = 8.4$ Hz, H-8), 8.02 (dd, 1H, $J = 8.1$ Hz, 1.5 Hz, H-4), 8.89 (dd, 1H, $J = 4.0$ Hz, 1.6 Hz, H-2) ppm. Anal ($C_{13}H_9N$) C, H, N.

6.1.10. 6-(3,4-Dihydro-2*H*-pyrrol-5-yl)quinoline (15). To a solution of **13** (2.98 g, 15.2 mmol) in CH_3CN (90 mL) and H_2O (20 mL), $PdCl_2$ (0.43 g) was added and the mixture heated at 80 °C for 3.5 h. After cooling, the mixture was treated with Et_2O, washed first with a saturated water solution of NaCl and then with dil NH_4OH, dried (Na_2SO_4) and evaporated, obtaining the title compound in 67% yield. Yellow solid, mp 115–120. This compound was used as such for the following step.

[^{1}H] NMR (400 MHz, $CDCl_3$, δ) 2.12 (m, 2H, C–CH_2–C), 3.08 (m, 2H, CH_2C═), 4.15 (m, 2H, CH_2N), 7.44 (dd, 1H, $J = 8.2$ Hz, 4.2 Hz, H-3), 8.12 (d, 1H, $J = 8.8$ Hz, H-7), 8.18 (d, 1H, $J = 1.5$ Hz, H-5), 8.21 (d, 1H, $J = 7.8$ Hz, H-8), 8.32 (dd, 1H, $J = 8.8$ Hz, 1.9 Hz, H-4), 8.95 (dd, 1H, $J = 4.2$ Hz, 1.6 Hz, H-2) ppm. [^{13}C] NMR (50 MHz, $CDCl_3$, δ) 22.86 (t), 35.05 (t), 61.86 (t), 121.65 (d), 127.79 (d), 127.94 (s), 128.38 (d), 129.72 (d), 132.84 (s), 136.77 (d), 149.22 (s) 151.33 (d), 172.70 (s) ppm.

6.1.11. 6-(Pyrrolidin-2-yl)quinoline (16). To a solution of compound **15** (0.05 g, 0.26 mmol) in absolute ethanol (100 mL), cooled at −70 °C, $NaBH_4$ (0.03 g, 0.79 mmol) was added portionwise. The reaction was allowed to warm to room temperature, then the mixture was concentrated under vacuum, treated with NaOH 0.1 M and extracted with CH_2Cl_2. After drying (Na_2SO_4) and removal of the solvent, 0.05 g of a residue was obtained, which was purified by transformation into the oxalate salt by treatment with oxalic acid in ethyl acetate. Mp 192–194 °C. Yield 72%.

[^{1}H] NMR (400 MHz, D_2O, δ) 2.17–2.42 (m, 3H), 2.59–2.68 (m, 1H), 3.49–3.75 (m, 2H), 4.96 (dd, 1H, J = 9.2 Hz, 7.2 Hz, CHN), 8.01 (dd, 1H, J = 8.4 Hz, 5.2 Hz, H-3), 8.12 (d, 1H, J = 8.8 Hz, H-7), 8.26 (d, 1H, J = 8.8 Hz, H-8), 8.32 (s, 1H, H-5), 9.02 (d, 1H, J = 8.4 Hz, H-4), 9.10 (d, 1H, J = 4.8 Hz, H-2) ppm. [^{13}C] NMR-APT (100 MHz, D_2O, δ) 23.44, 30.24, 45.76, 62.34, 122.39, 122.48, 128.19, 128.75, 133.16, 136.09, 138.65, 145.83, 146.47, 167.27 ppm. Anal. ($C_{15}H_{16}N_2O_4$) C, H, N.

6.1.12. 6-(1-Methylpyrrolidin-2-yl)quinoline (5). To a solution of **16** (0.15 g, 0.76 mmol) in a mixture of 2 M Na_2CO_3 (3.68 mL) and dioxane (1 mL), kept at 0 °C, NaOH (0.6 mL) and benzyl chloroformate (1.2 equiv) were added dropwise at the same time. After 1 h stirring at 0 °C, the mixture was treated with H_2O and extracted with CH_2Cl_2. Anhydrification and removal of the solvent gave a residue (0.18 g), which was dissolved into anhydrous DME (1 mL) and added dropwise to a suspension of $LiAlH_4$ (0.085 g, 2.2 mmol) in an. DME (1 mL) at 0 °C. After 30 min stirring, the excess hydride was destroyed with H_2O and the mixture extracted with CH_2Cl_2. Drying (Na_2SO_4) and removal of the solvent gave a residue, which was purified by column chromatography, giving the title compound as an oil (80% yield).

[^{1}H] NMR (400 MHz, $CDCl_3$, δ) 1.78–1.92 (m, 2H), 1.96–2.08 (m, 1H), 2.22 (s, 3H, NMe), 2.22–2.32 (m, 1H), 3.23–3.33 (m, 2H, 2CHN), 7.38 (dd, 1H, J = 8.3 Hz, 4.2 Hz, H-3), 7.72–7.78 (m, 2H, H-5, H-7), 8.08 (d, 1H, J = 8.5 Hz, H-8), 8.13 (d, 1H, J = 8.3 Hz, H-4), 8.87 (dd, 1H, J = 4.2 Hz, 1.7 Hz, H-2) ppm. [^{13}C] NMR-APT ($CDCl_3$, δ) 22.71, 35.24, 40.58, 57.14, 71.34, 121.07, 125.74, 128.24, 129.39, 129.63, 135.83, 141.82, 147.99, 149.97 ppm. Anal. ($C_{14}H_{16}N_2$) C, H, N. The compound was transformed into the oxalate salt by reaction with 1 equiv of oxalic acid in ethyl acetate, obtaining a deliquescent solid. [^{1}H] NMR (400 MHz, D_2O, δ) 2.30–2.39 (m, 2H, CH_2); 2.42–2.53 (m, 1H, CH); 2.81 (s, 3H, NCH_3); 3.35–3.42 (m, 1H, CHN); 3.90–3.96 (m, 1H, CHN); 4.69 (dd, 1H, J = 10 Hz, 7.6 Hz, CHN); 8.13 (dd, 1H, J = 7.2 Hz, 6.8 Hz, H-3); 8.22 (dd, 1H, J = 8.8 Hz, 1.6 Hz, H-7); 8.35 (d, 1H, J = 9.2 Hz, H-8); 8.46 (s, 1H, H-5); 9.18–9.19 (m, 2H, H-2 + H-4) ppm.

6.1.13. 1,1-Dimethyl-2-(quinolin-6-yl)pyrrolidinium iodide (17). Compound **5** was dissolved in amylene-stabilized $CHCl_3$ and 1 equiv of MeI was added. The mixture was left stirring at room temperature in the dark for 48 h, then the solvent was removed, the residue was dissolved in the minimum amount of EtOH and precipitated with Et_2O. The white solid was collected and dried: 80% yield. The solid decomposed without melting at T >180 °C.

[^{1}H] NMR (400 MHz, D_2O, δ) 2.36–2.46 (m, 2H), 2.60–2.72 (m, 1H), 2.76 (s, 3H, NMe), 2.79–2.88 (m, 1H), 3.13 (s, 3H, NMe), 3.77 (dt, 1H, J = 12.0 Hz, 9.4 Hz, CHN), 3.87 (dt, 1H, J = 12.0 Hz, 6.2 Hz, CHN), 4.95 (dd, 1H, J = 11.4 Hz, 7.8 Hz, CHN), 7.62 (dd, 1H, J = 8.4 Hz, 4.4 Hz, H-3), 7.72–7.78 (dd, 1H, J = 9.0 Hz, 2.2 Hz, H-7), 8.09 (d, 1H, J = 8.8 Hz, H-8), 8.18 (d, 1H, J = 2.0, H-5), 8.41 (d, 1H, J = 8.0 Hz, H-4), 8.89 (dd, 1H, J = 4.4 Hz, 1.6 Hz, H-2) ppm. [^{13}C] NMR-APT (100 MHz, D_2O, δ) 19.13, 26.07, 45.13, 50.79, 66.23,78.37, 121.44, 127.20, 127.86, 128.50, 130.87, 131.99, 138.18, 147.26, 151.94 ppm. Anal. ($C_{15}H_{19}IN_2$)C, H, N.

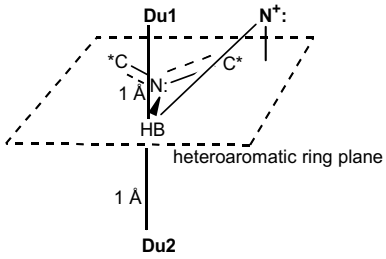


Figure 3. Fitting points (in bold) used to align PHT, **1** and **2** as shown in Figure 2.

6.2. Pharmacology

The new compounds were tested according to the previously published protocol.[42] Amines were tested as oxalate salts.

6.3. Molecular modeling

The molecular models were built using the program InsightII2000 and energy minimized using Discover (cvff force-field).[25]

The molecular models of PHT, **1** and **2** were superimposed on the template (PHT), using, as fitting points, the cationic nitrogen $\overset{+}{N}$ and two dummy points (Du1 and Du2) located ±1 Å along the normal to the heteroaromatic ring plane passing through the HB site (Fig. 3). This type of alignment allowed us to superimpose molecules using only two pharmacophore points.

Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2004.10.039.

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